European guidelines for quality assurance in colorectal cancer screening and diagnosis

cancer screening and diagnosis

First Edition

European Commission

Cover

Upper left: surgically excised pT2 adenocarcinoma of the rectum

Upper middle: depressed carcinoma (0-IIc), 7mm, submucosal invasion

Upper right: same lesion, chromoscopy with indigocarmine solution

Centre left: tubular adenoma at initial stage, 12 mm, HE stain

Centre middle: depressed carcinoma (0-IIa+IIc), 10 mm, massive submucosal invasion, HE stain

Centre right: tubulovillous adenoma giving rise to a pY1 adenocarcinoma invading the polyp stalk and showing vascular invasion. Completely excised

Lower left: Large colonic tubulovillous adenoma, surgically excised due to size

Lower middle: sessile adenocarcinoma (0-Is), 13 mm, superficial distorted vessels, submucosal invasion

Lower right: sessile adenoma (0-Is), 8 mm, chromoscopy with indocarmine solution

European Commission

European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition

ERRATA Version 1. Updated 23 August 2012.

The following errata apply to the first version of the Guidelines that was made available on the website of the European Union in February 2011. They will be corrected in the second print version of the Guidelines.

p. LIII, Systematic reviews – quorum checklist: *Replace*: methological quality *by*: quality of conduct

p. VI   *Replace*: Henning Erfkampf *by*: Henning Erfkamp

pp. VII, 145 & 146   *Replace*: Ernst Kuipers *by:* Ernst J. Kuipers

p. XLVI, point 7   *Delete*: after positive FS

p. LII, Bibliographic review: *Replace 1st sentence by:* The Literature Group conducted bibliographic searches using MeSH terms and free text words. For most clinical questions searches were limited to the years 2000 to 2008 and were performed on Medline, and in many cases also Embase and the Cochrane library databases

p. LVII, last column of Table 1, row with evidence level II: *Replace:* C *by*: Nc

p. LVIII, last paragraph, 1ˢᵗ sentence: *Insert:* many of *after:* because

p. 24   *Replace:* von BE *by:* von Benzon E,

p. 45, 3ʳᵈ para.   *Delete:* Wardle, *in:* Wardle, Weinberg et al. 2004 *Replace:* Miles & Atkin 2005 *by:* Wardle, Miles & Atkin 2005

p.63, p.100   *Replace:* van BM *by:* van Ballegooijen M,

p. 91, 1ˢᵗ & 2ⁿᵈ-to-last paragraph: *Replace:* Shoenfeld et al. 2005 *by:* Schoenfeld et al. 2005

p. 98, 5ᵗʰ para.   *Insert:* 'comma' after: over-diagnosis of cancer,

p. 100   *Replace:* de VE *by:* De Vries E,

p. 106 Rec 4.8   *Replace:* contradicting *by:* contradictory

p. 107 Rec 4.10, p122 1ˢᵗ line *Replace:* denaturation *by:* degradation

p. 111, 3ʳᵈ para.   *Replace:* Scottish population *by:* Scottish programme

p. 114, 3ʳᵈ para.   *Replace:* the concentration *by:* the Hb concentration

p. 114, 7ᵗʰ para.   *Replace*: PK isoenzyme type M2 has shown poor sensitivity and specificity when used alongside two immunochemical devices (Mulder et al 2007). *By*: When used alongside guaiac-based or immunochemical devices, PK isoenzyme type M2 has not shown adequate specificity for population screening (Shastri et al. 2006; Möslein et al 2010).

p. 118, 1ˢᵗ para.   *Replace:* US FDA Centre for Device *by:* US FDA Center for Devices

p. 118, last para.   *Replace:* taking aspirin. *by:* taking aspirin or NSAIDs.

p. 120, Table 4.3   *Replace:* phenybutazone *by:* phenylbutazone

p. 131, 2nd-to-last para. *Delete:* comma *in:* Levi et al 2006 compared,

p. 132, 2nd line	*Replace:* (Flexsure) *by:* (FlexSure)
p. 133	*Replace:* Rossum *by:* van Rossum and colleagues
p. 141	*After:* Lamph SA, Bennitt WE, Brannon CR & Halloran SP (2009), Evaluation report: Immunochemical faecal occult blood tests *Replace:* Report no.09042. *by:* . Guildford: Centre for Evidence-based Purchasing; 2009. Report no. CEP09042. http://nhscep.useconnect.co.uk/cepproducts/catalogue.aspx
	Insert: Möslein G, Schneider C, Theilmeier A, Erckenbrecht H, Normann S, Hoffmann B, Tilmann-Schmidt D, Horstmann O, Graeven U & Poremba C (2010), [Analysis of the statistical value of various commercially available stool tests - a comparison of one stool sample in correlation to colonoscopy], *Dtsch.Med Wochenschr.*, vol. 135, no. 12, pp. 557-562.
p. 142	*Delete*: Mulder SA, van Leerdam ME, van Vuuren AJ, Francke J, van Toorenenbergen AW, Kuipers EJ & Ouwendijk RJ (2007), Tumor pyruvate kinase isoenzyme type M2 and immunochemical fecal occult blood test: performance in screening for colorectal cancer, Eur.J.Gastroenterol.Hepatol. vol. 19, no. 10, pp. 878-882.
	After: Piper MA (2004), Immunochemical versus Guaiac fecal occult blood tests. *Replace:* Blue Cross Blue Shield Technology Evaluation Center Assessment Programme, *by:* Chicago, IL, USA: Blue Cross and Blue Shield Association, Technology Evaluation Center. TEC Assessment Programs, vol. 19, no. 5.
p. 143	*Insert*: Shastri YM, Naumann M, Oremek GM, Hanisch E, Rosch W, Mossner J, Caspary WF & Stein JM (2006), Prospective multicenter evaluation of fecal tumor pyruvate kinase type M2 (M2-PK) as a screening biomarker for colorectal neoplasia, *Int J Cancer*, vol. 119, no. 11, pp. 2651-2656.
p. 194, last line	*Replace:* Sect 6.7 *by:* Rec 6.7
p. 220, 1st para.	*After:* muscularis mucosae *insert:* 'full stop' This
p. 258, 2nd para.	*Replace:* or nylon loop *by:* or a nylon loop
p. 259, 2nd para.	*Replace:* Rothnet *by:* Rothnet®
p. 273	*Replace:* Wolf Schmiegel *by:* Wolff Schmiegel
p. 274	*Replace:* Marten Rasmussen *by*: Morten Rasmussen
p. 276, 281, 285 & 290	*Replace:* Figure 1*by*: Figure 9.1
p. 313, 5th para.	*Insert:* one *after:* compared to a non-tailored
p. 332, 2nd para. & p. 335, 10th ref.	*Replace:* (European Cancer Network 2008) *by*: (European Commission 2008)

European Commission

European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition

27 July 2012

Addendum

For a journal publication, the authors, contributors, editors and reviewers were requested to review their declarations of interest based on the new IARC procedures adopted since publication of the original Guidelines book. The following revised declarations were received:

Dr Hermann Brenner is employed by The German Cancer Research Center (DKFZ) that has received significant research support from Eiken Chemicals (less than 40 000 €) for previously and currently running studies on colorectal cancer detection. The following companies have provided the DKFZ with faecal occult blood tests free of charge for previously and currently running evaluation studies: ulti med, Ahrensburg, Germany; DIMA, Gottingen, Germany; Beckman Coulter, Krefeld, Germany; CAREdiagnostica, Voerde, Germany; Preventis, Bensheim, Germany; Quidel, San Diego, California. The total value of the non-monetary support is less than 100 000 €.

Dr Christian Pox has received lecture honoraria and travel support of less than 7 000 € from the following manufacturers of pharmaceuticals, diagnostics, medical equipment and other health products: Dr Falk Pharma, Hitachi and Roche. He has also received consultancy fees of 1 500 € for attending an Advisory Board Meeting of the Abbot company, a broad-based health care manufacturer, and 2 100 € from the AQUA Institute, Germany, a private entity dedicated to quality assurance research and implementation that is mandated by the Federal Committee of the German Statutory Health Insurance System to implement a nationwide quality assurance scheme.

Dr Wolff Schmiegel is the holder of one patent and the co-holder of three patents covering technologies related to screening and diagnosis of colorectal tumours. He is also co-holder of a patent covering substances potentially suitable for prevention and treatment of colorectal polyps. He has received consultancy fees of less than 2 000 € from Astra Zeneca and consultancy fees, lecture honoraria and travel support totalling less than 16 000 € from Roche. He has also received lecture honoraria from Abbott, Pfizer and Falk. The Medical Faculty of the Ruhr University in Germany where he works has received institutional research funding of less than 165 000 € from Roche and the pharmaceutical manufacturer Sanofi Aventis for studies in colorectal cancer screening and diagnosis. Dr Schmiegel is the sole shareholder (25 000 €) of Medmotive GmbH, a holding that until 2010 controlled 25% of the company Westdeutsches Darm-Centrum GmbH with a capital investment of 25 000 €. The aim of these companies is to develop and coordinate a quality-assured network in colorectal oncology through such activities as consulting, development of therapeutic standards, specialized training and lobbying key stakeholders.

Dr Graeme Young has received consultancy fees (less than 10 000 €) from Quidel Corporation, a manufacturer of diagnostic products. Eiken Chemicals has provided Flinders University where he works with faecal occult blood tests free of charge for studies (total value less than 10 000 €).

European guidelines for quality assurance in colorectal cancer screening and diagnosis *First Edition*

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Luxembourg: Publications Office of the European Union, 2010

Joan Austoker (1947 – 2010)

This edition is dedicated to the memory of our colleague and friend Joan Austoker who contributed substantially to the development of the European cancer screening guidelines through her pioneering work in communication in cancer screening and prevention.

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Minor pertinent interests are not listed. These include stock holdings valued at less than US$ 10 000 overall and occasional travel grants totalling less than 5% of time, and consulting on non-regulatory matters totalling less than 2% of time and compensation.

Conflicts of interest have been disclosed by the experts between October 2008 and October 2010. No other potential conflicts of interest relevant to this publication were reported.

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Prefaces

Preface

John Dalli*

Colorectal cancer is the second most common newly diagnosed cancer and the second most common cause of cancer death in the EU. Many of these deaths, however, could be avoided through early detection, by making effective use of screening tests followed by appropriate treatment.

For this reason, the evidence-based European Code Against Cancer recommends that men and women from 50 years of age should participate in colorectal screening. This has been given effect within the EU by the 2003 Council Recommendation on cancer screening. Making this screening effective, in turn, depends on appropriate quality assurance at all levels.

That is the aim of the "European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis". These guidelines, the result of tireless efforts over many years by a wide range of European experts, represent a major achievement, with the potential to add substantial value to the efforts of the Member States to improve control of colorectal cancer.

This, in turn, will save lives and help improve the quality of life of millions of EU citizens, their families and friends.

This publication will ensure that any organisation, programme or authority in the Member States, as well as every European citizen, can gain access to the recommended standards and procedures. It represents a concrete contribution by the European Commission to our shared European objective of preventing human illness and disease.

I should like to thank the editors, authors, contributors and reviewers of these guidelines for assembling, analysing and documenting the enormous quantity of evidence on which this volume has been based. I am confident that it will become an indispensable guide for colorectal cancer screening in the coming years.

Brussels, July 2010

*European Commissioner for Health and Consumer Policy

Preface

Christopher Wild*

Colorectal cancer is the third most common in incidence and the fourth most common cause of cancer death worldwide, with an estimated 1.2 million new cases and 609 000 deaths in 2008. Based on demographic trends, the annual incidence is expected to increase by nearly 80% to 2.2 million cases over the next two decades and most of this increase will occur in the less developed regions of the world. These regions are ill equipped to deal with the rapidly increasing demand for cancer treatment resulting from population growth and higher life expectancy. Even greater increases in the worldwide burden of the disease can be expected if less developed regions adopt a more "westernised" life style. Concerted efforts to control colorectal cancer are therefore of increasing importance worldwide.

Fortunately, experience in Europe has shown that systematic early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, particularly if they are effectively integrated into an overall programme of comprehensive cancer control. Coordinated resources are needed not only for screening and primary prevention programmes but also for further development and capacity building in diagnosis and therapy of colorectal cancer, especially in the less developed regions of the world because of the expected changes mentioned above. Political commitment and appropriate investment at an early stage are not only likely to lower the future burden of disease, but also to save considerable resources when organised, population-based programmes are fully established.

The authors and editors of the new European quality assurance guidelines have taken care to point out that organised as opposed to "opportunistic" screening programmes are recommended because they include an administrative structure responsible for programme implementation, quality assurance and evaluation. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each person in the eligible target population. Personal invitation aims to give each eligible person an equal chance of benefiting from screening and to thereby reduce health inequalities. These efforts should be supported by effective communication for groups with limited access to screening, such as less advantaged socio-economic groups. This, in turn, should permit an informed decision about participation, based on objective, balanced information about the risks and benefits of screening. The population-based approach to programme implementation is also recommended because it provides an organisational framework for effective management and continuous improvement of the screening process, such as through linkage with population registers and cancer registries for optimization of invitation to screening and for evaluation of screening performance and impact respectively. In this context research after implementation of screening should be an integral part of population-based programmes.

Crucial to the success of any cancer screening programme is the availability of comprehensive, evidence-based quality assurance guidelines, addressing all of the steps in the screening process, including not just performance of a test, but also information and invitation, diagnostic work-up of lesions detected in screening, treatment, surveillance and any other subsequent care. Widespread application of the standardised indicators recommended in the Guidelines will facilitate quality management and promote the international exchange of information and experience between programmes that is essential for continuous quality improvement.

Finally, as Director of an international agency I would like to highlight the outstanding international cooperation that has gone into the preparation of these Guidelines. But also, as the landscape of cancer occurrence evolves to cast the burden of colorectal cancer on new regions facing increasing incidence rates due to an aging population and "westernised" life style, it is vital that the excellence demonstrated here is pursued and translated to appropriate guidance for the widest possible audience on a global scale.

Lyon, October 2010

*Director, International Agency for Research on Cancer

Preface

Jean-François Rey, Colm O'Morain, René Lambert

Quality assurance has always been a key issue in digestive endoscopy. Fortunately, this important topic has recently also been placed high on the agenda of the health authorities, healthcare providers and patient associations. A major reason for this is the increasing awareness that effective screening programmes will have a vital role to play in helping to cope with growing problem of colorectal cancer in Europe. Effective screening should supplement ongoing efforts to improve primary prevention, as well as the diagnosis and therapy of symptomatic disease. However, the potential of screening to reduce the burden of the most common cancer in Europe will require an enormous expansion in the number of people attending national programmes. That in turn will require substantial resources and expanded efforts in the field of quality assurance.

Colonoscopy plays a key role in every colorectal cancer screening programme because it is the gold standard by which the status of people with positive screening tests is evaluated. The same applies to patients in a symptomatic service. As pointed out in the new European Guidelines, efforts to improve quality and expand screening should be well planned and should lead to improvement not just in screening, but also in symptomatic care. These efforts should also have a positive impact on the availability of high quality endoscopy for symptomatic services, by providing sufficient resources to achieve and maintain appropriate waiting times.

The international collaboration and cooperation in developing the new European Guidelines for quality assurance in colorectal cancer screening and diagnosis has also shown that additional tools are now being developed to assist gastroenterologists in evaluating their current level of performance in screening. It should be kept in mind, however, that these initiatives, though important, can only be effective if they stimulate action to continuously improve and maintain high levels of professional performance.

The following factors remain fundamental to achieving high quality in endoscopy:

Thorough cleansing of the large bowel is the first mandatory step. If the endoscopist's vision is obscured, small or flat lesions anywhere in the colon and particularly sessile lesions in the right colon may go undetected.

Patient tolerance and acceptance of the endoscopic examination is also of prime importance and can be increased by sedation. National or cultural differences in this domain should be taken into account.

Training, adequate equipment and external evaluation of endoscopy units has proved to be essential during the start-up of a national screening programme. Such activities are likely to play an increasingly important role in quality assurance of symptomatic endoscopy in the coming years.

Nice, Ireland, Lyon, October 2010

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Preface

J Patnick, N Segnan, L von Karsa (Editors)

The editorial board would like to thank all the authors, reviewers and other contributors who have worked so hard to develop these first Guidelines for the new colorectal screening cancer screening programmes which are emerging across the EU. This has been a major undertaking since many of these chapters broke new ground in European collaboration and challenged established practice. The chapters have been produced to a new evidence-based protocol that will, from now on, be used across all EU cancer screening guidelines and this also presented the authors and reviewers with fresh challenges.

It is, however, fair to say that the production has been a very stimulating experience to those involved, and the evolution of the guidelines created strong bonds for future joint working.

The guidelines are designed to ensure that in the future each Member State can deliver screening to a high standard even if they are at the beginning of a screening programme. There is another thank you due. This is to the citizens of the EU and those patients on whose past experiences of screening and endoscopy these guidelines are based.

Oxford, Turin, Lyon, October 2010

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Executive summary

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Role of screening in colorectal cancer control

Colorectal cancer (CRC) is the most common newly-diagnosed cancer and the second most common cause of cancer deaths in Europe. In the 27 Member States of the European Union, CRC ranks second in incidence and mortality in both sexes, with approximately 330 000 new cases and 149 000 deaths estimated for men and women combined in 2008 (Ferlay, Parkin & Steliarova-Foucher 2010). Even in those Member States in the lower range of age-standardised rates of CRC, the burden of disease is significant compared to other regions of the world (see Ferlay et al. 2010). CRC is therefore an important health problem across the EU.

The aim of screening is to lower the burden of cancer in the population by discovering disease in its early latent stages. This permits more effective treatment than if diagnosed later when symptoms occur. Early treatment of invasive lesions, for example by endoscopic resection of early CRC, can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Randomised trials in people of average risk invited to attend screening have shown a reduction in CRC mortality (Hardcastle et al. 1996; Kronborg et al. 1996; Mandel et al. 1999; Atkin et al. 2010) and incidence (Mandel et al. 2000; Atkin et al. 2010).

Council Recommendation on cancer screening

The potential of screening for improving control of CRC has been recognised by the Council of the European Union. On 2 December 2003 the Council recommended implementation of population-based screening programmes using evidence-based tests for breast, cervical and colorectal cancer to the EU Member States (Council of the European Union 2003) (Appendix 2). The Council Recommendation fulfils the criteria for screening defined by the World Health Organization (Wilson & Jungner 1968) and takes into account the substantial experience in implementation of population-based cancer screening programmes in the EU. The Recommendation spells out fundamental principles of best practice in early detection of cancer. It invites EU Member States to take common action to implement cancer screening programmes with an organised, population-based approach and appropriate quality assurance at all levels, taking into account European quality assurance Guidelines for cancer screening, where they exist (von Karsa et al. 2008).

By the end of 2007, ten EU Member States were in the process of implementing national population-based CRC screening programmes (Cyprus, Finland, France, Hungary, Italy, Poland, Portugal, Romania, Slovenia and the United Kingdom) (see Appendix 3 (Commission of the European Communities 2008)). Furthermore, seven Member States had established nationwide non-population-based programmes. In the meantime, ten Member States have newly established or have upgraded the status of their existing CRC screening programmes (Czech Republic, France, Ireland, Lithuania, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom). In addition, Denmark and the Netherlands are currently in the decision process for implementing population-based CRC screening programmes.

Need for effective quality assurance

The potential harm caused by CRC screening includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost, and exposure to the risk of invasive procedures for detection and diagnosis as well as for removal of lesions detected in screening. As demonstrated in implementation of breast and cervical cancer screening programmes, overall screening outcome and quality depend on the performance at each step in the screening process. To achieve the potential benefit of CRC screening, quality must therefore be optimal at each step in the process. This includes identification and personal invitation of the target population, performance of the screening test and, if necessary, diagnostic work-up, treatment, surveillance and aftercare of screen-detected lesions (Perry et al. 2008; von Karsa et al. 2010; Arbyn et al. 2010).

Screening is performed on predominantly healthy people; comprehensive quality assurance is also required to maintain an appropriate balance between benefit and harm in the large numbers of people eligible to attend cancer screening programmes. The Council of the European Union therefore recommends appropriate, comprehensive quality standards and best practice in the implementation of cancer screening programmes. European quality assurance Guidelines for breast and cervical cancer screening have been developed by experts and published by the EU (European Commission 2006; European Commission 2008). The availability of the new European guidelines for quality assurance in colorectal cancer screening and diagnosis will now make similar standards available to the Member States in which colorectal cancer screening programmes are currently running or being established.

Primary screening test recommended by the EU

The Council Recommendation calls for introduction of new cancer screening tests in routine healthcare only after they have been evaluated in randomised controlled trials (RCTs). To date, only the faecal occult blood test (FOBT) for men and women aged 50–74 years has been recommended by the EU for CRC screening (Appendix 2). In addition, any screening policy for colorectal cancer should take into account the available evidence and the numerous other principles and standards of best practice laid down in the Council Recommendation. Although the use of endoscopic screening methods is increasing, the majority of colorectal cancer screening examinations performed in the EU use the evidence-based test recommended by the Council of the EU.

Purpose of the EU quality assurance Guidelines

The purpose of the new EU Guidelines is not to recommend other modalities that might currently also be suitable for CRC screening in the EU. Instead, the Guidelines provide guiding principles and evidence-based recommendations on the quality assurance that should be followed when implementing screening programmes using the various modalities currently adopted in publicly mandated CRC screening programmes in the Member States.

The Editors have been conscious of the importance of raising and maintaining quality standards across all the EU Member States. While never abandoning those standards and recommendations that are crucial for mortality reduction, we have as far as possible attempted to achieve an equitable balance that can be used across a wide spectrum of cultural and economic healthcare settings. As with any standards and recommendations, these should be continuously reviewed in the light of future experience. It is not the purpose of these guidelines to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. Neither should this edition be regarded as a textbook or in any way a substitute for practical clinical training and experience.

The Guidelines have been developed to inform European policymakers and public health specialists, and any other interested parties about the essential issues, guiding principles, standards and procedures of quality assurance and best practice that should be taken into account in running and establishing colorectal cancer screening programmes in the EU Member States.

The Guidelines have been specifically developed for screening of the average-risk population in which most CRC develops. High-risk individuals should be referred for high-risk protocols if available. Since the relative variation in the moderate risk of developing CRC in most people with a family history of CRC is less than the geographic variation in average risk between the Member States, no attempt was made to develop recommendations tailored to this subgroup of the population. However, in the absence of hereditary syndromes people identified with a family history of CRC should not be excluded from average risk screening (see Chapter 2). The potential benefit and harm of screening recommendations tailored to people with a positive family history could be examined in greater depth in the preparation of the next edition of the Guidelines.

Process of guideline development

The Guidelines have been developed in an international collaborative project that was co-financed by the EU Public Health Programme.[10] The project involved over 90 experts serving as authors, contributors, editors or reviewers from 32 countries including 21 EU Member States 13 of which acceded to the EU before 2004 (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Portugal, Spain, Sweden, the Netherlands and the United Kingdom) and eight of which acceded later to the EU (Czech Republic, Hungary, Latvia, Lithuania, Malta, Poland, Romania and Slovenia), as well as one EU applicant country (Croatia). The other countries represented among the collaborators included Argentina, Australia, Canada, China, India, Israel, Japan, Korea, Norway and the United States of America.

The new EU quality assurance Guidelines build on the successful developments in previous editions of the other EU screening Guidelines. The comprehensive CRC Guidelines cover the entire screening process from invitation to management of screen-detected lesions. Although the Guidelines focus on elements essential to screening, it is recognised that certain principles are equally important in diagnosis. Training, multi-disciplinary teamwork, monitoring and evaluation, cost-effectiveness, minimising adverse effects, and timeliness of further investigations are referred to repeatedly throughout the chapters. The applicability of many of the recommended standards and procedures to quality assurance in both screening and diagnosis is therefore reflected in the title of the first edition. Variations in style and emphasis have been unavoidable given the diverse sources of the contributions. However, the editors have maintained a high degree of conformity of approach.

The process used for identifying and evaluating the relevant evidence and for developing respective recommendations in the new Guidelines is described in detail in the section on *Principles of evidence assessment and methods for reaching recommendations*. Briefly, scientific and editorial management was provided by an editorial board with extensive experience in development of best practice guidelines, in evaluation of strategies for CRC screening and in programme management. The editorial board drafted an initial comprehensive outline of the Guidelines and recruited a multidisciplinary group of experts from across Europe to collaborate in revising the outline and drafting the chapters of the guideline according to an agreed methodology.

Additional scientific support was provided by a Literature Group consisting of epidemiologists with special expertise in the field of CRC and in critical appraisal of clinical studies. The Literature Group worked closely with the authors and editors in preparing and conducting systematic reviews of the literature on clinical questions of key importance. Bibliographic searches were conducted for the time period extending from January 2000 to December 2008. Some articles published between 2000 and 2008 and not retrieved by the systematic search were considered to be relevant by the authors. Those references have therefore been included in the body of evidence with the agreement of the editorial board. In addition, articles published after December 2008 that were judged of high relevance by the authors and editors were also included in the Guidelines evidence base.

Preliminary versions of the draft guidelines were repeatedly reviewed and revised through multi-disciplinary meetings of the authors, editors and the Literature Group, as well as in pan-European network meetings with participants from all of the EU Member States.

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[10] Grant agreement No 2005317: Development of European Guidelines for Quality Assurance of Colorectal Cancer Screening. Partner institutions: Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom; Unit of Cancer Epidemiology, Centre for Cancer Epidemiology and Prevention (CPO) and S. Giovanni University Hospital, Turin, Italy; Public Association for Healthy People, Budapest, Hungary; European Cancer Patient Coalition (ECPC), Utrecht, Netherlands ; Quality Assurance Group, Section of Early Detection and Prevention, International Agency for Research on Cancer, Lyon, France.

Guideline publication format

The print version of the Guidelines (400 pages) consists of 10 chapters each of which includes a list of key recommendations at the beginning of the chapter. The recommendations are graded according to the strength of the recommendation and the supporting evidence (for scale see below). The respective evidence is also summarised in the body of the chapters, with explicit citation of over 750 references in the Guidelines. In total, over 250 recommendations are provided.

The version of the Guidelines provided on the internet (web version) includes all of the elements in the print version, as well as an extensive Appendix 1 in digital format (1000 pages) with a complete record of the key clinical questions and corresponding bibliographic searches conducted by the Literature Group. The search results are documented in table format, and in summary documents. Altogether summary documents for over 100 clinical questions, and over 500 evidence tables are provided.

The level of evidence and the strength of each of the key recommendations presented in the front of each chapter is indicated using the following grading scales:

For the **level of evidence**:

I	multiple randomised controlled trials (RCTs) of reasonable sample size, or systematic reviews (SRs) of RCTs
II	one RCT of reasonable sample size, or 3 or less RCTs with small sample size
III	prospective or retrospective cohort studies or SRs of cohort studies; diagnostic cross sectional accuracy studies
IV	retrospective case-control studies or SRs of case-control studies, time-series analyses
V	case series; before/after studies without control group, cross sectional surveys
VI	expert opinion

For the **strength of the respective recommendation:**

A	intervention strongly recommended for all patients or targeted individuals
B	intervention recommended
C	intervention to be considered but with uncertainty about its impact
D	intervention not recommended
E	intervention strongly not recommended

Images illustrating the chapter on *Quality assurance in pathology in colorectal cancer screening and diagnosis* will be provided on a virtual pathology website at: http://www.virtualpathology.leeds.ac.uk.

Scope of recommendations in the Guideline chapters

The numerous guiding principles, evidence-based recommendations and conclusions presented in the new EU Guidelines for quality assurance in colorectal cancer screening and diagnosis cannot all be presented here. In addition to the key aspects of screening policy and methodology already mentioned above, the following points are highlighted in order to illustrate the scope and depth of the recommendations and conclusions in the first edition.

Chapter 1 - Evidence for the effectiveness of colorectal cancer screening

The first chapter deals with the currently available evidence for the effectiveness of CRC screening, key operational parameters (age-range, interval between two negative screening examinations, or

some combinations of tests) and cost-effectiveness. Among other things, the discussion of the 17 graded recommendations presented in the chapter reveals that the most evidence is available for the primary screening test (FOBT) recommended by the EU.

Chapter 2 - Organisation of colorectal screening programmes

The 29 recommendations and conclusions in Chapter 2 deal with key organisational aspects that influence the quality and effectiveness of CRC screening. There is a broad consensus in the EU on the fundamental principle that a colorectal cancer screening programme is a multidisciplinary undertaking. The effectiveness of the programme is a function of the quality of the individual components of the process.

It is also recognised that the provision of the screening service must account for the values and preferences of individuals as well as the perspectives of public health. The public health perspective in the planning and provision of screening services requires commitment to ensuring equity of access and sustainability of the programme over time. Taking into account the perspective of the individual requires commitment to promoting informed participation and to providing a high quality, safe service.

Successful implementation of a screening programme entails more than simply carrying out the screening tests and referring individuals to assessment whenever indicated. Specific protocols must also be developed for identifying and subsequently inviting the target population. Protocols are also required for patient management in the diagnosis, treatment, and surveillance phases in order to ensure that all individuals have timely access to the proper diagnostic and treatment options.

Irrespective of the organisational approach, it should be recognised that appropriate political and financial support is crucial to the successful implementation of any screening programme.

Chapter 3 - Evaluation and interpretation of screening outcomes

Chapter 3 includes 20 graded recommendations on the processes and procedures required for effective monitoring and evaluation of CRC screening programmes. Of fundamental importance is the complete and accurate recording of all relevant data on each individual and every screening test performed - including the test results, the decisions made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death.

The chapter also provides an overview of performance measurements currently available from published trial results and population-based screening programmes. Based on this evidence and experience in implementation of population-based screening programmes, the authors and editors were able to reach a consensus on recommended standards of acceptable and desirable performance for a number of parameters. These initial standards, as well as the relevant standards available from other chapters are presented in a table at the end of the Executive Summary. The numbering of the standards is not indicative of importance. As explained elsewhere in the Guidelines, programmes should monitor numerous additional parameters in order to maintain and continuously improve quality. It is hoped that adherence to the other recommendations in the Guidelines will lead to development of a database that permits future expansion and improvement of the current standards.

Chapter 4 - Faecal occult blood testing

Chapter 4 includes 21 detailed and in some cases complex recommendations dealing with design and application of faecal occult blood tests in CRC screening. It is recognised that the ideal biochemical test for population-screening of colorectal cancer would use a biomarker, specific and sensitive for both cancer and pre-cancer, on an easily collected sample, that could be safely and cheaply transported to a centralised laboratory for accurate, reproducible, and inexpensive automated analysis. In addition to these factors which are important for test performance, other key aspects should be taken into account that may influence the acceptability of the test in the target population. These include

the design of the test kit, the instructions provided with the kit and the manner in which it is distributed. Laboratory quality assurance and external quality assessment also play an important role.

Chapter 5 - Quality assurance in endoscopy

Chapter 5 provides a comprehensive view of the many-faceted aspects of quality assurance in endoscopy in its use both for the follow-up of screen-positives as well as for primary screening.[11] The complexity of the relevant issues is reflected by the comparatively large number of specific recommendations dealing with planning and location of endoscopic services, infrastructure and equipment, preparation of the patient and aftercare, endoscopic technique, performance of endoscopists, quality improvement, policies and processes; a total of 50 recommendations.

The organisation of the chapter follows the patient journey to provide an explanation of the relevant issues of quality assurance that can also be used to improve the acceptability of CRC screening. This approach reflects the fundamental consensus of the authors and editors that everyone undergoing endoscopy, whether for primary screening, for assessment of abnormalities detected in screening, for assessment of symptoms, or for surveillance, should have as pleasant an experience as possible. A positive experience will help encourage people to recommend screening, assessment and surveillance to their friends, family and colleagues.

It is also recognised that the screening service must take into account the perspectives of endoscopy as well as public health to ensure that the experience is high-quality, safe and efficient as well as person-oriented. Furthermore, screening should take account of historic developments within different local and cultural contexts.

Although primary screening endoscopy is less complex than follow-up endoscopy (of screen-positives) primarily because of the lower frequency of high-risk lesions in primary screening endoscopy, care must be taken to ensure that the introduction of screening does not compromise endoscopy services for symptomatic patients and that screening and symptomatic (diagnostic) services achieve the same minimum levels of quality and safety. It is also recognised that, wherever possible, the quality assurance required for screening should have an enhancing effect on the quality of endoscopy performed for symptomatic patients and for other reasons. As for the other chapters in these Guidelines, the authors of chapter 5 have emphasised that screening and diagnosis of appropriate quality requires a multidisciplinary approach to diagnosis and management of lesions detected during endoscopy.

Chapter 6 - Professional requirements and training

Chapter 6 provides 23 graded recommendations dealing with the requisite competency of screening staff. As previously mentioned with regard to the other chapters in the Guidelines, the fundamental need for a multidisciplinary approach and hence the need for special training of the multidisciplinary team that is responsible for a colorectal screening programme is recognised.

All staff involved in the delivery of a colorectal cancer screening programme require knowledge of the basic principles of colorectal cancer screening. The need for specialist training in screening differs between the different disciplines and is most important for those involved in the delivery of the service and diagnosis, e.g. laboratory staff, endoscopists, radiologists, pathologists and nurses. The surgical treatment of screen-detected cancer and post-operative treatment is not performed differently according to whether a cancer is screen detected or symptomatic, but there are certain considerations for the surgeon to take into account when treating a screen-detected cancer. Professional requirements of oncologists are not discussed in this chapter because, stage for stage, their role in the treatment of screen-detected disease is no different from that in symptomatic disease.

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[11] Note that although endoscopic screening programmes are running in some Member States, the FOBT is the only CRC screening test currently recommended by the EU (Appendix 2).

Chapter 7 - Quality assurance in pathology

The present chapter suggests practical guidelines for pathology within a colorectal screening programme. The pathology service plays a very important role in colorectal cancer screening since the management of participants in the programme depends on the quality and accuracy of the diagnosis. Pathology affects the decision to undergo further local and/or a major resection as well as surveillance after screening. The adoption of formal screening programmes leads to improvement not only in the management of early but also of advanced disease through the introduction of guidelines, quality standards, external quality assurance and audit. In screening programmes, the performance of individuals and programmes must be assessed and it is advantageous if common diagnostic standards are developed to ensure quality, recognise areas where sufficient evidence is still lacking, and initiate high-quality studies to gather the evidence required.

Chapter 7 includes 23 graded recommendations concentrating on the areas of clinical importance (Quirke et al. 2010). It is hoped that these recommendations will also help to standardise quality and performance across the European Union. The associated annex deals with some of the more difficult areas and suggests topics for future research (Vieth et al. 2010). Guidelines for the reporting and management of resected specimens have been included in an attempt to move towards agreed minimum European standards of pathology in these areas as well. This is the first edition of what will be a continuing process of revision as new data emerge on the pathology, screening and management of colorectal cancer. It is also hoped that by setting minimum standards, these will be followed in all programmes and that this will encourage the development of higher standards amongst the pathology community and screening programmes.

Chapter 8 - Management of lesions detected in colorectal cancer screening

The inclusion of a chapter with 32 graded recommendations on management of lesions detected in CRC screening recognises that reduction in CRC mortality is the main endpoint of any CRC screening programme. It is also recognised that all screening modalities will detect substantial numbers of individuals with adenomas (Levin et al. 2008) as well as a lesser number of lesions in the serrated pathway, some of which should be treated as adenomas (see Ch. 7). As adenomas are recognised to be pre-malignant (Leslie et al. 2002) screening has the potential to reduce the incidence of the disease if these lesions are adequately managed. To achieve the dual aims of mortality and incidence reduction it is essential that all the elements of the screening service achieve and maintain high levels of quality. The screening process can only be successful if it is followed by timely and appropriate management of screen-detected lesions.

In essence, the management of screen-detected adenomas and carcinomas does not differ, stage for stage, from that required for symptomatic disease. However, screening detects a different spectrum of disease compared with that diagnosed in the symptomatic population (i.e. higher proportion of early disease). Thus, there are some considerations in the management of screen-detected disease that should be emphasised. In this Chapter of the Guidelines the management of endoscopically detected pre-malignant lesions, pT1 cancers, as well as colon cancer and rectal cancer which is not limited to the submucosa are dealt with separately and discussion is focused on issues pertinent to screening. For these reasons, adjuvant chemotherapy and the management of advanced disease are not discussed.

Of prime general importance is the wide consensus that colorectal neoplasia is best managed by a multi-disciplinary team. The relevant disciplines include: surgery, endoscopy, pathology, radiology, radiotherapy, medical oncology, specialist nursing, genetics and palliative care (SIGN 2003), which should work in close collaboration with primary care. Furthermore, it is recognised that the interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards have been set which aim at minimising delay (NHS 2007). Also of relevance in this regard is the recognition that colonoscopy is not merely a diagnostic procedure, but has therapeutic

capacity (Cotton & Williams 1996), and it is essential that the endoscopist carrying out screening colonoscopy has the necessary expertise to remove all but the most demanding lesions (see also Chapter 5).

Chapter 9 - Colonoscopic surveillance following adenoma removal

Chapter 9 includes 24 graded recommendations and a comprehensive strategy for surveillance after removal of adenomas in people taking part in screening programmes in any Member State. The recommendations in the EU Guidelines recognise that people with previous adenomas are at increased risk for recurrent adenomas and thus eventually colorectal cancer (Atkin, Morson & Cuzick 1992). The risk depends mainly on findings during baseline colonoscopy, in particular the number, size and histological grade of removed adenomas. This allows categorisation of patients into different risk groups. The indication and interval for surveillance is determined primarily by the presumed risk for recurrence of advanced adenomas and cancer, and secondarily by age, co-morbidity, and patient wishes.

The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage. It must be kept in mind however, that colonoscopy is a costly, invasive and scarce resource. Therefore, colonoscopy surveillance should be undertaken only in people at increased risk, and at a minimum frequency required to provide adequate protection against the development of cancer. If colonoscopy surveillance is undertaken, it should be performed to the highest standard.

Because surveillance colonoscopy consumes considerable endoscopic resources it may prevent a country that has difficulty meeting demand from sustaining reasonable waiting times. Screening programmes should therefore have a policy on surveillance with a hierarchy of action for different risk groups based on resource availability. The policy may limit surveillance to the high risk group if sufficient resources are not available to include people with lower risk.

Chapter 10 - Communication

Chapter 10 provides 35 recommendations dealing with communication in CRC screening. The large body of guidance reflects the essential goal of CRC screening programmes which is to reduce the burden of illness and death due to colorectal cancer. Screening programmes can only be successful if they ensure that as many people in the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend CRC screening. As adverse effects are intrinsic to screening practice, participants should understand that a balance exists between benefits and harms associated with CRC screening (Holland, Stewart & Masseria 2006). A key component of CRC screening programmes, therefore, is the information and education provided about CRC, and CRC screening tests and procedures.

The recommendations in the EU Guidelines reflect the wide consensus that people who use CRC screening services should receive accurate and accessible information that reflects the most current evidence about the CRC screening test and its potential contributions to reducing illness as well as information about its risks and limitations. Achieving this goal is challenging, due to the complexity of CRC screening programmes compared to other established programmes such as screening for breast or cervical cancer. In CRC screening multiple tests are currently in use (FOBT in most, as well as flexible sigmoidoscopy (FS) and colonoscopy in some Member States). Furthermore, some screening tests are invasive, and have known adverse effects. Finally, some CRC screening procedures are generally undertaken without supervision from a healthcare professional (FOBT screening test and bowel cleansing procedure in preparation for follow-up colonoscopy or endoscopy screening). Therefore specific instructions on how to use the FOBT kit or perform the bowel cleansing procedure need to be communicated to the patient.

The recommendations in the chapter on Communication have therefore been developed to give people involved in providing and/or managing CRC screening (e.g. managers, decision-makers, health professionals etc.) an insight into the complexity of communication in CRC screening and its related critical issues. Pragmatic recommendations are also provided on information strategies/tools/interventions that can be used in current or future programmes. These recommendations mainly refer to an organised (and centralised) CRC screening programme, as this represents the gold standard to achieve (see Chapters 1 and 2). In the Communication chapter, the authors specifically provide guidance for screening programmes based on the primary screening test recommended by the EU, the faecal occult blood test (FOBT, see Chapter 4) which is also the most frequently used test in programmes implemented by the Member States. Most of the recommendations can be applied to endoscopy programmes as well.

Performance standards

The following Summary Table presents the performance standards in the first edition of these Guidelines. The numbering is not indicative of importance; more complete information regarding definition and context is provided in the sections indicated. As explained in the Guidelines, programmes should monitor numerous additional parameters in order to maintain and continuously improve quality. The standards listed in the present Summary Table are based on an overview of performance measurements currently available from published trial results and population-based screening programmes (see Chapter 3). In light of this evidence and experience in implementation of population based screening programmes, the authors and editors of the current version of the Guidelines were able to reach a consensus on the recommended targets across the EU. On occasions we have had to accept that different disciplines and different Member States show some variation of priorities and target levels. In all cases we have attempted to list what we regard as the most generally appropriate professionally agreed levels for usage in a pan-European setting. In any case, all targets should be constantly reviewed in the light of experience and revised accordingly with regard to results achieved and best clinical practice. As far as possible, targets given refer to men and women aged 50–74 years invited to and/or attending a CRC screening programme.

Summary Table of performance standards in colorectal cancer screening

	Indicator[1]	Acceptable level	Desirable level
1	Invitation coverage[Rec 3.7; Sect 3.3.1]	95%	>95%
2	Uptake rate[Rec 3.8; Sect 3.3.1]	>45%	>65%
3	Rate of inadequate FOBT[Rec 3.9; 4.21; Sect 3.3.2; 4.3.4]	<3%	<1%
4	Maximum time between test and receipt of result should be 15 days[Rec 3.15; Sect 3.3.4]	>90%	
5	Rate of referral to follow-up colonoscopy after positive test [Rec 3.10; Sect 3.3.2, 3.3.3]	90%	>95%
6	Maximum time between referral after positive screening (any modality) and follow-up colonoscopy should be 31 days [Rec 3.16, 5.19; Sect 3.3.4, 5.3.5]	>90%	>95%
7	Compliance with follow-up colonoscopy after positive FS [Rec 3.14; Sect 3.3.2, 3.3.3]	85%	>90%
8	Rate of complete colonoscopies. Follow-up and screening colonoscopies to be recorded separately [Rec 3.11; Rec 5.41, Sect 3.3.2, 3.3.3, 5.4.5.1]	>90%	>95%
9	Time interval between positive colonoscopy/FS and definitive management should be within 31 days [Rec 3.17, 8.2; Sect 3.3.4, 8.2]	>95%	
10	Endoscopists participating in a CRC screening programme should perform a minimum no. of procedures per year [Rec 5.38; Sect 5.4.5.1]	300	>300
11	Biopsies and lesions identified in the screening programme and the subsequent resection specimen should be reported on a proforma[Rec 7.11; Sect 7.6.5.2, 7.8]	>90%	
12	Rate of high-grade neoplasia reported by pathologists in a colonoscopy screening programme[Rec 7.21; Sect 7.7]	<5%	
13	Rate of high-grade neoplasia reported by pathologists in a FOBT screening programme[Rec 7.21; Sect 7.7]	<10%	

[1] **Sect** (superscript) refers to the section/s of the Guidelines dealing with the respective indicator.

Rec (superscript) refers to the number of the corresponding recommendation in the Guidelines.

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Principles of evidence assessment and methods for reaching recommendations

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Introduction

The evidence-based process for development of the recommendations in the first edition of the European Guidelines for quality assurance in colorectal cancer screening and diagnosis was established at the outset of the project in 2006 by an editorial board with extensive experience in development of best practice guidelines, in evaluation of strategies for colorectal cancer (CRC) screening and in programme management. In 2007 the editorial board drafted an initial comprehensive outline of the Guidelines and recruited a multidisciplinary group of experts in colorectal cancer screening and diagnosis across the European Union to collaborate in revising the outline and drafting the chapters, including guiding principles and recommendations. Additional scientific support was provided by a Literature Group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews.

The expert Literature Group provided technical and scientific support to the authors and editors in searching the relevant literature, assessing the methodological quality of retrieved studies, defining a grading system of the level of evidence and strength of the recommendations, and preparing evidence tables and summary documents for over 500 references identified through systematic reviews of the literature according to the priorities and procedures agreed with the editorial board and the authors.

The Literature Group was coordinated by N. Segnan at the Unit of Cancer Epidemiology, Department of Oncology of the Piedmont Centre for Cancer Prevention (CPO Piemonte) and S. Giovanni University Hospital, Turin, Italy, and was lead by S. Minozzi at the same institution. Other members of the Literature Group were based at the CPO in Turin and at the Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, Oxford, United Kingdom. Additional scientific and technical support was provided by the International Agency for Research on Cancer, Quality Assurance Group, Section of Early Detection and Prevention, Lyon, France.

The principles of evidence assessment and the methods for developing the recommendations presented in the Guidelines are described below. The contribution of the Literature Group was crucial to the feasibility of this resource-intensive process. In addition to the above-mentioned activities, it included assistance to the chapter authors in defining relevant clinical questions of key importance.

The clinical questions for which evidence was collected by the Literature Group and the results of the literature search and analysis conducted by the group are presented in Appendix 1 to the Guidelines. The appendix is only available in electronic format, due to the extensive size of the records that correspond to approximately 1 000 printed pages.

The editors of the first edition of the Guidelines hope that this approach will promote regular updating of the evidence-based Guidelines and that resources will be available in the future to expand the current evidence base and the respective documentation, as well as to improve the methods that have been followed.

Definition of clinical questions

In multidisciplinary workshops conducted in 2007 and 2008 the chapter authors met with the editorial board and the Literature Group. At these meetings, the table of contents of the Guidelines was repeatedly revised and the methodology of evidence-based guideline development, including the process of identifying and evaluating the relevant evidence for each chapter based on the topics in the revised outline was agreed with the authors. Subgroups of authors responsible for each chapter also worked individually with members of the Literature Group to develop clinically relevant questions based on the revised chapter outlines, and the results for each chapter were subsequently discussed with the entire group of authors and editors and the Literature Group in plenary workshop sessions in order to ensure a common methodological approach and to reach a consensus on questions of key

importance requiring the support of the Literature Group in order to identify and assess the relevant evidence. This collaborative, multidisciplinary approach remained a guiding principle throughout the entire process up to completion of drafting and editing of the Guideline chapters.

The clinical questions initially formulated by the authors of each chapter and subsequently agreed with the editorial board and the other authors were developed according to the PICOS method (Greenhalgh 1997; O'Connor, Green & Higgins 2008; Richardson et al. 1995) modified slightly to take into account the aim of screening to lower the burden of the disease in the population:

P: **patients/population** characteristics

I: experimental **intervention** on which the question is focused

C: **comparison** intervention / control /reference group

O: **outcome** measure relevant for the clinical question

S: **study** design on which to base the evidence search

The extensive list of initial clinical questions was reduced to a feasible number, by prioritising questions of key importance for each chapter. In total, 113 clinical questions were prioritised. The PICOS components of each prioritised question were subsequently used by the Literature Group to define specific key words that were then employed in comprehensive bibliographic searches. The results of these activities were reported back to the authors and editors in subsequent workshops and electronically. This enabled the editors and authors to provide continuous professional and scientific support to the process of identifying and analysing the relevant evidence.

Bibliographic review

The Literature Group performed bibliographic searches on Medline, Embase, and the Cochrane library databases from January 2000 to December 2008 using mesh terms and free text words. Searches were conducted without date restrictions if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Published articles suggested by the authors and not retrieved by a systematic search, were also considered. Only scientific publications in English, Italian, French and Spanish were included. Priority was given to recently published, systematic reviews or clinical guidelines. If systematic reviews of high methodological quality were retrieved, the search for primary studies was limited to those published after the last search date of the most recently published systematic review (i.e. if the systematic review had searched primary studies until February 2006, primary studies published after February 2006 were sought). If no systematic reviews were found, a search for primary studies published since 2000 was performed.

In selected cases references not identified by the above process were included in the evidence base, i.e. when authors of the chapters found relevant articles published after 2008 during the period when chapter manuscripts were drafted and revised prior to publication. The criteria for relevance were: articles concerning new and emerging technologies where research is growing rapidly, high quality and updated systematic reviews, and large trials that make a significant contribution to the robustness of the results or allow upgrading of the level of evidence.

Inclusion criteria

The inclusion criteria applied by the Literature Group were based on the highest level of available evidence, taking into account study design. For primary studies, for each kind of question (e.g., effectiveness, diagnostic accuracy, acceptability and compliance) a hierarchy of the study designs and inclusion/exclusion criteria was developed by the epidemiologists in the Literature Group. For example, for effectiveness studies randomised controlled trials (RCT) were initially searched for. If RCTs were

retrieved, no other types of study design were considered. If no, or only a few and/or small RCTs were retrieved, quasi-experimental studies were considered. If no quasi-experimental studies were found, prospective or retrospective cohort and case-control studies were considered. If studies with none of the above designs were retrieved, cross-sectional studies and case series were included. For diagnostic accuracy questions, cross-sectional studies with verification by reference standard were considered as the best source of evidence.

Quality assessment

The methodological quality of the publications retrieved by the Literature Group was assessed using the following criteria obtained from published and validated check lists.

Systematic reviews - quorum checklist

A validated checklist for evaluating the manner in which systematic reviews have been conducted was not available when the methods for the present EU Guidelines were established. Therefore the QUOROM checklist that assesses the quality of reporting was used as a proxy to assess the methodological quality of systematic reviews. This approach reflects the view that the quality of reporting can be used as a criterion for the quality of the process of preparing a systematic review (Moher et al. 1999).

Randomised Controlled Trials

Randomised controlled trials were assessed using the following criteria suggested in the Cochrane Handbook {Higgins, 2008 754 /id} and by the Cochrane Effective Practice and Organisation of Care Review Group {EPOC, 2002 755 /id}:

- Unit of allocation (i.e. who or what was allocated to study groups: individuals or clusters);

- Unit of analysis (i.e. results analysed as events at the level of individuals or clusters);

- If unit of allocation and unit of analysis differ, was cluster analysis performed?

- Protection against selection bias (adequate sequence generation and allocation concealment);

- Protection against performance bias (blinding of providers);

- Protection against contamination (blinding of participants);

- Protection against attrition bias (intention to treat analysis, few lost at follow up balanced between groups); and

- Protection against detection bias (blinding of participants and outcome assessors).

Observational studies: cohort studies and case control studies

Observational studies were evaluated using the following criteria of the Newcastle-Ottawa Scale (for recent overview see: (Wells et al. 2010)

- Case control studies:
  - o Adequate definition of the cases;
  - o Representativeness of the cases;
  - o Selection source of controls;
  - o Definition of controls;
  - o Comparability of cases and controls on the basis of the design or analysis;
  - o Method of exposure assessment;

- o Same method of ascertainment for cases and controls;
- o Non-Response rate.

- Cohort studies:
    - o Representativeness of the exposed cohort;
    - o Selection source of the non-exposed cohort;
    - o Method of exposure assessment;
    - o Demonstration that outcome of interest was not present at start of study;
    - o Comparability of cohorts on the basis of the design or analysis;
    - o Method outcome assessment;
    - o Adequacy of follow up of cohorts.

Interrupted time series studies

Studies based on interrupted time series were assessed using the following criteria suggested by the Cochrane Effective Practice and Organisation of Care Review Group (EPOC 2002):

- Clearly defined point in time when the intervention occurred.
    - o A: Intervention occurred at a clearly defined point in time;
    - o B: NOT CLEAR because not reported in the paper;
    - o C: Intervention did not occur at a clearly defined point in time.

- At least three data points before and three after the intervention.
    - o A: Three or more data points before and three or more data points recorded after the intervention;
    - o B: NOT CLEAR because not reported in the paper;
    - o C: Less than three data points recorded before, and less than three data points recorded after intervention.

- Protection against secular changes (the intervention is independent of other changes).
    - o A: Intervention occurred independently of other changes over time;
    - o B: NOT CLEAR because not reported in the paper;
    - o C: Intervention was not independent of other changes over time.

- Protection against detection bias (intervention unlikely to affect data collection).
    - o A: Intervention unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention);
    - o B: NOT CLEAR because not reported in the paper;
    - o C: Intervention likely to affect data collection (for example, any change in source or method of data collection before vs. after the intervention).

- Blinded assessment of primary outcome(s).
    - o A: Explicit statement of authors that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;
    - o B: NOT CLEAR if not specified;
    - o C: Outcomes were not assessed blindly.

- Completeness of data set.

  o A: Data set covers 80-100% of total number of participants or episodes of care in the study;

  o B: NOT CLEAR if not specified;

  o C: Data set covers less than 80% of the total number of participants or episodes of care in the study.

Diagnostic accuracy studies

The criteria used to evaluate diagnostic accuracy studies were obtained from the QUADAS checklist (Whiting et al. 2003):

- Study design: diagnostic cross-sectional studies with prospective or retrospective recruitment; case control;

- Spectrum of patients representative of the individuals who will receive the test in practice;

- Patients selection criteria clearly described;

- Verification by reference standard of all or a randomised sample of subjects (absence of verification bias);

- Execution of the index and comparator tests adequately described;

- Execution of the reference standard adequately described;

- Independent and blind interpretation of index test and reference standard results;

- Un-interpretable /intermediate test results reported;

- Withdrawals from the study explained.

Clinical guidelines

The quality of clinical guidelines evaluated by the Literature Group was assessed using the following most relevant criteria derived from the COGS checklist (Shiffman et al. 2003):

- Description of the clinical specialisation of the members of the panel of guideline authors;

- Search strategy described (databases, years covered, any language restriction);

- Inclusion criteria of primary studies stated;

- Method used to analyse and synthesise the evidence and to reach the consensus among the panellists to elaborate the recommendation described;

- Presence of a grading of level of evidence and/or of the strength of the recommendation; and

- Presence of a complete reference list.

Evidence tables and summary documents

The Literature Group prepared the following documents based on the publications retrieved for each clinical question or group of clinical questions. The documents were subsequently used by the authors in drafting respective chapters:

- An evidence table for each retrieved study with the main characteristics of the study (study design, objective of the study, comparisons, participant's characteristics, outcome measures, results, methodological quality, level of evidence);

- A summary document with a synthesis of the number, types and characteristics of the retrieved studies, their overall methodological quality, a description of the main methodological flaws, the study results and the conclusions and the overall level of evidence.

Evidence tables were not prepared for: additional publications cited in the background sections of the chapters; pathological and clinical classifications; technical instructions; narrative reviews; editorials and personal communications; and articles published before 2000 and cited by the authors after the systematic search of the literature.

Some articles published between 2000 and 2008 and not retrieved by the systematic search were considered to be relevant by the authors. Those references have therefore been included in the body of evidence in agreement with the editorial board. For these articles, evidence tables were prepared after December 2009, but the respective results were not included in the summary documents.

The above documents, together with the clinical questions and respective bibliographic literature searches for each chapter, are documented in Appendix 1.

Grading system

The key recommendations presented in each chapter of the Guidelines are listed at the front of the respective chapter together with a grading of the evidence on which each recommendation is based, and the strength of the recommendation. Only the highest level of evidence supporting a recommendation is reported. The following grading scales are used:

Level of the evidence

- **I:** multiple randomised controlled trials (RCTs) of reasonable sample size, or systematic reviews (SRs) of RCTs
- **II:** one RCT of reasonable sample size, or 3 or less RCTs with small sample size
- **III:** prospective or retrospective cohort studies or SRs of cohort studies; diagnostic cross sectional accuracy studies
- **IV:** retrospective case-control studies or SRs of case-control studies, time-series analyses
- **V:** case series; before/after studies without control group, cross sectional surveys
- **VI:** expert opinion

Strength of the recommendations

The strength of recommendations was graded according to the following scale:

- **A:** intervention strongly recommended for all patients or targeted individuals
- **B:** intervention recommended
- **C:** intervention to be considered but with uncertainty about its impact
- **D:** intervention not recommended
- **E:** intervention strongly not recommended

The strength of each key recommendation was determined by the authors of each chapter in agreement with the Guidelines editorial board.

Following the list of key recommendations at the beginning of each chapter, the rationale and the evidence on which the recommendations are based is summarised in the body of the chapter, including the respective levels of evidence.

In a number of chapters, in addition to the key recommendations, fundamental statements (Guiding Principles) defining the aims and scope of the recommendations presented in the chapter are provided at the front of the text. Most of the Guiding Principles are considered to be self-evident. All reflect the

consensus of the authors and editors on essential principles of best practice in screening and diagnosis of colorectal cancer. In addition to these principles, additional advisory statements are made in the body of the chapters that are not specifically graded. These statements also represent the consensus of the authors and editors on best practice.

Correspondence between level of evidence and strength of recommendation

This present grading of the strength of recommendations did not require a rigid correspondence with the levels of evidence. For example grade **A** was given to interventions for which there was evidence level **I** (multiple RCTs or SR of RCTs) but also to interventions that could not be assessed by RCTs, (e.g. psychological aspects, the importance of an accurate information to the patients, etc). Grade **B** was given to interventions with lower evidence level (**II** or **III**) but also for interventions with evidence level **I** but with uncertainty about their impact in the population or about practical implementation (e.g. lack of resources for implementation, social barriers, supposed lack of acceptability by the target population). Grade **C** level was given to interventions for which evidence was not available or was of low grade (i.e. **IV**, **V**) or that may not have been considered of high importance for other reasons (i.e. psychological or social aspects). Grades **D** and **E** were assigned to interventions for which there was evidence of no benefit for participants, or for which the harm outweighed the benefits.

Table 1   Correspondence between level of evidence and strength of recommendations

		Strength of recommendation				
		A	**B**	**C**	**D**	**E**
Levels of evidence	**I**	C	C		C	C
	II	Nc	C		C	C
	III	Nc	C	C	C	Nc
	IV	Nc	Nc	C	Nc	Nc
	V	Nc	Nc	C	Nc	Nc
	VI	Nc	Nc	C	Nc	Nc

C: Coherence between the level of evidence and the strength of recommendations

Nc: No coherence between the level of evidence and the strength of recommendations

Method of obtaining consensus between the chapter authors and editors and the internal peer review

Each subgroup of authors responsible for a chapter received all the evidence tables and summary documents relating to the respective clinical questions. The authors drafted each chapter by describing the relevant issues, summarising the evidence, and including recommendations and conclusions. The authors also proposed a grading for the strength of the evidence and the strength of the respective recommendations, based on the results of the literature search and on their clinical experience, as well as any additional pertinent scientific literature that was taken into account with agreement from the editorial board. The draft chapters and the proposed strength of each recommendation were discussed with the editorial board and the authors of all chapters to reach consensus.

External peer review

Chapter drafts were subsequently sent to international experts in their respective fields for external peer review. They were also made available for web consultation with restricted access by experts involved in screening programmes. Comments and criticisms were considered and a final version of the chapters was elaborated. Preliminary and nearly final versions of the Guidelines chapters were prepared and discussed at pan-European network meetings of screening experts, clinicians, advocates, healthcare planners and regulators from all of the EU member states and two EU applicant countries in 2008 and 2009.

Final editing

During 2010, final changes resulting from the network discussion in November 2009 were taken into account by the authors of respective chapters. The consistency of the recommendations between the individual chapters was reviewed by the editorial board and corrections were made where necessary.

The editors recognise that the approach to collection of the relevant evidence adopted for the Guidelines may have permitted introduction of bias if the authors or editors were not aware of significant publications after December 2008 because the systematic searches performed by the Literature Group were limited to this date. However, the relevant publications of studies published after 2008 that have been cited by the authors to justify recommendations have been evaluated by the Literature Group and respective evidence tables are included in Appendix 1. In view of the qualifications and experience of the authors and editors and the transparency of the process of guideline development, the editors have concluded that further efforts to limit this potential bias would have little or no impact on the content of the final recommendations. As mentioned in the introduction, the editors hope that the approach to evidence-based guideline development adopted for the first edition of the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis will promote systematic discussion of the evidence base for the Guidelines and that resources will be available in the future to continuously update and expand the current evidence base and the respective documentation.

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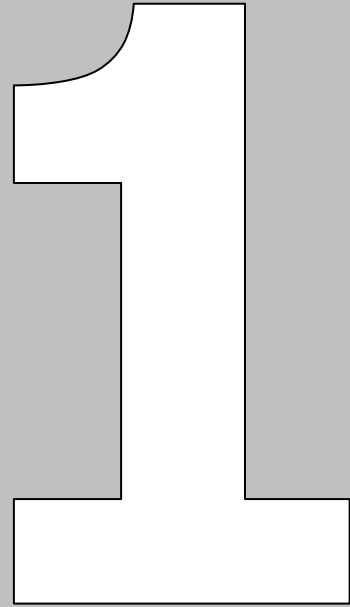
Introduction

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Guiding principles

1. The aim of screening as a tool for cancer control is to lower the burden of cancer in the population by discovering latent disease in its early stages and treating it more effectively than if diagnosed later when symptoms have appeared.

2. As such, screening is a commendable method to reduce the burden of disease. However, population screening targets a predominantly healthy population, and should therefore only be conducted after a careful consideration of both harms and benefits.

3. In 1968 the World Health Organisation (WHO) defined the first set of principles for population screening (Wilson & Jungner 1968). These principles are still valid today. Together with the substantial experience in implementation of population-based screening programmes in the EU, they have been taken into account in the Council Recommendation on Cancer Screening of 2 December 2003.

4. The Council Recommendation spells out fundamental principles of best practice in early detection of cancer and invites EU Member States to take common action to implement cancer screening programmes with an organised, population-based approach and with appropriate quality assurance at all levels, taking into account European quality assurance guidelines for cancer screening, where they exist.

5. The Council Recommendation calls for introduction of new cancer screening tests in routine healthcare only after they have been evaluated for efficacy in randomised controlled trials (RCTs) and after other relevant aspects such as cost-effectiveness in the different healthcare systems have been taken into account. Only the FOBT for men and women aged 50-74 years has been recommended for CRC screening by the EU to date.

6. Any screening policy for colorectal cancer should also take into account the available evidence and the numerous other principles and standards of best practice laid down in the Council Recommendation.

7. The overwhelming majority of colorectal cancer screening examinations performed in the EU use the primary screening test recommended by the Council of the European Union; the Faecal Occult Blood Test (FOBT). The purpose of the European Guidelines for Quality Assurance in Colorectal Cancer Screening is not to provide recommendations on which other modalities might now be suitable for CRC screening in the EU. Instead, the new European Guidelines provide guiding principles and evidence-based recommendations on the quality assurance which should be followed when implementing CRC screening using the various modalities currently adopted in publically mandated programmes in the EU Member States.

Recommendations and conclusions[1]

Guaiac FOBT

1.1   There is good evidence that invitation to screening with FOBT using the guaiac test reduces mortality from colorectal cancer (CRC) by approximately 15% in average risk populations of appropriate age **(I)**.[Sect 1.2.1.1]

1.2   RCTs have only investigated annual and biennial screening with guaiac FOBT (gFOBT) **(II)**. To ensure effectiveness of gFOBT screening, the screening interval in a national screening programme should not exceed two years **(II - B)**.[Sect 1.2.1.2]

1.3   Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years **(IV)**. The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources **(VI - B)**.[Sect 1.2.1.3]

Immunochemical FOBT

1.4   There is reasonable evidence from an RCT **(II)** that iFOBT screening reduces rectal cancer mortality, and from case control studies **(IV)** that it reduces overall CRC mortality.[Sect 1.2.2.1] Additional evidence indicates that iFOBT is superior to gFOBT with respect to detection rate and positive predictive value for adenomas and cancer (see also Ch. 4, Rec. 4.2) **(III)**.[Sect 1.2.2.1; 4.2.5; 4.3; 4.4.2]

1.5   Given the lack of additional evidence, the interval for iFOBT screening can best be set at that of gFOBT, and should not exceed three years **(VI - C)**.[Sect 1.2.2.2]

1.6   In the absence of additional evidence, the age range for a screening programme with iFOBT can be based on the limited evidence for the optimal age range in gFOBT trials (see Rec. 1.3) **(VI - C)**.[Sect 1.2.2.3; 1.2.1.3]

Sigmoidoscopy

1.7   There is reasonable evidence from one large RCT that flexible sigmoidoscopy (FS) screening reduces CRC incidence and mortality if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs **(II)**.[Sect 1.3.1.1]

1.8   The available evidence suggests that the optimal interval for FS screening should not be less than 10 years and may even be extended to 20 years (see Rec. 1.11) **(IV - C)**.[Sect 1.3.1.2; 1.3.2.2]

1.9   There is limited evidence suggesting that the best age range for FS screening should be between 55 and 64 years **(III − C)**. After age 74, average-risk FS screening should be discontinued, given the increasing co-morbidity in this age range **(V - D)**.[Sect 1.3.1.3]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

Colonoscopy

1.10   Limited evidence exists on the efficacy of colonoscopy screening in reducing CRC incidence and mortality **(III)**. However, recent studies suggest that colonoscopy screening might not be as effective in the right colon as in other segments of the colorectum **(IV)**.^{Sect 1.3.2.1}

1.11   Limited available evidence suggests that the optimal interval for colonoscopy screening should not be less than 10 years and may even extend up to 20 years **(III - C)**.^{Sect 1.3.2.2}

1.12   Indirect evidence suggests that the prevalence of neoplastic lesions in the population below 50 years of age is too low to justify colonoscopic screening, while in the elderly population (75 years and above) lack of benefit could be a major issue. The optimal age for a single colonoscopy appears to be around 55 years **(IV - C)**. Average risk colonoscopy screening should not be performed before age 50 and should be discontinued after age 74 **(V - D)**.^{Sect 1.3.2.3}

Combination of FOBT and sigmoidoscopy

1.13   The impact on CRC incidence and mortality of combining sigmoidoscopy screening with annual or biennial FOBT has not yet been evaluated in trials. There is currently no evidence for extra benefit from adding a once-only FOBT to sigmoidoscopy screening **(II)**.^{Sect 1.4}

New screening technologies under evaluation

1.14   There currently is no evidence on the effect of new screening tests under evaluation on CRC incidence and mortality **(VI)**. New screening technologies such as CT colonography, stool DNA testing and capsule endoscopy should therefore not be used for screening the average-risk population **(VI - D)**.^{Sect 1.5}

Cost-effectiveness

1.15   Costs per life-year gained for both FOBT and endoscopy screening strategies are well below the commonly-used threshold of US$ 50 000 per life-year gained **(III)**.^{Sect 1.1.2.4; 1.2.2.4; 1.3.1.4; 1.3.2.4}

1.16   There is some evidence that iFOBT is a cost-effective alternative to gFOBT **(IV)**.^{Sect 1.2.2.4}

1.17   Available studies differ with respect to what screening strategies are most cost-effective. No recommendation of one screening strategy over the others can be made based on the available evidence of cost-effectiveness **(III - D)**.^{Sect 1.2.1.4}

1.1 Background

1.1.1 Colorectal cancer in Europe

Colorectal cancer (CRC) is an important health problem in Europe. Each year approximately 435 000 people are newly diagnosed with CRC (Ferlay, Parkin & Steliarova-Foucher 2010). About half of these patients die of the disease making CRC the second leading cause of cancer deaths in Europe.

CRC mortality varies among the 27 EU Member States, with Hungary having the highest mortality rates and Cyprus having the lowest (Table 1.1). At least part of the differences in CRC mortality can be explained by differences in lifestyle, screening practices and treatment between countries (von Karsa et al. 2010).

Table 1.1: Age-standardised (Europe) incidence and mortality rates for colorectal cancer by country and gender, rate per 100 000 in 2008 (data source: Ferlay, Parkin & Steliarova-Foucher 2010)

Country/Region	Females		Males	
	Incidence	Mortality	Incidence	Mortality
Austria	33.4	14.0	55.5	24.4
Belgium	42.3	15.5	66.3	22.7
Bulgaria	34.4	14.6	53.2	26.5
Cyprus	23.4	9.3	34.3	12.4
Czech Republic	44.3	19.1	91.2	40.3
Denmark	52.6	22.7	68.4	29.8
Estonia	32.8	16.7	47.7	29.0
Finland	29.1	11.0	41.4	16.8
France	36.4	14.0	54.8	23.0
Germany	41.5	15.4	68.5	25.0
Greece	17.1	10.1	24.7	14.6
Hungary	43.8	25.2	93.8	53.3
Ireland	42.9	15.4	66.9	27.9
Italy	43.7	14.3	68.3	23.6
Latvia	28.8	18.3	45.5	29.2
Lithuania	29.3	16.7	49.9	29.1
Luxembourg	38.1	13.2	63.8	22.1
Malta	29.9	18.0	47.9	25.8
Netherlands	25.7	15.7	49.3	29.8
Poland	34.4	16.6	61.6	30.6
Portugal	27.9	14.7	41.2	25.2
Romania	43.9	20.2	88.6	46.9
Slovakia	37.4	18.9	74.6	37.4
Slovenia	34.1	15.0	60.4	28.6
Spain	38.4	15.4	47.8	20.6
Sweden	46.2	18.5	65.1	26.0
United Kingdom	35.4	14.4	54.9	21.9

1.1.2   Population screening for colorectal cancer

CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas, according to the adenoma-carcinoma sequence (Figure 1.1) (Muto, Bussey & Morson 1975; Morson 1984). Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. Adenomas are most often polypoid, but can also be sessile or flat (Hofstad 2003). An adenoma grows in size and can develop high-grade neoplasia. At a certain point in time, the adenoma can invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms yet (preclinical). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. In developed countries, approximately, 40–50% of the population develop one or more adenomas in a lifetime (Hofstad 2003), but the majority of these adenomas will never develop into CRC. Only 5–6% of the population actually develop CRC (Jemal et al. 2008). The average duration of the development of an adenoma to CRC is unobserved, but is estimated to take at least 10 years (Winawer et al. 1997). This long latent phase provides an excellent window of opportunity for early detection of the disease.

Figure 1.1: Schematic overview of the adenoma-carcinoma sequence.
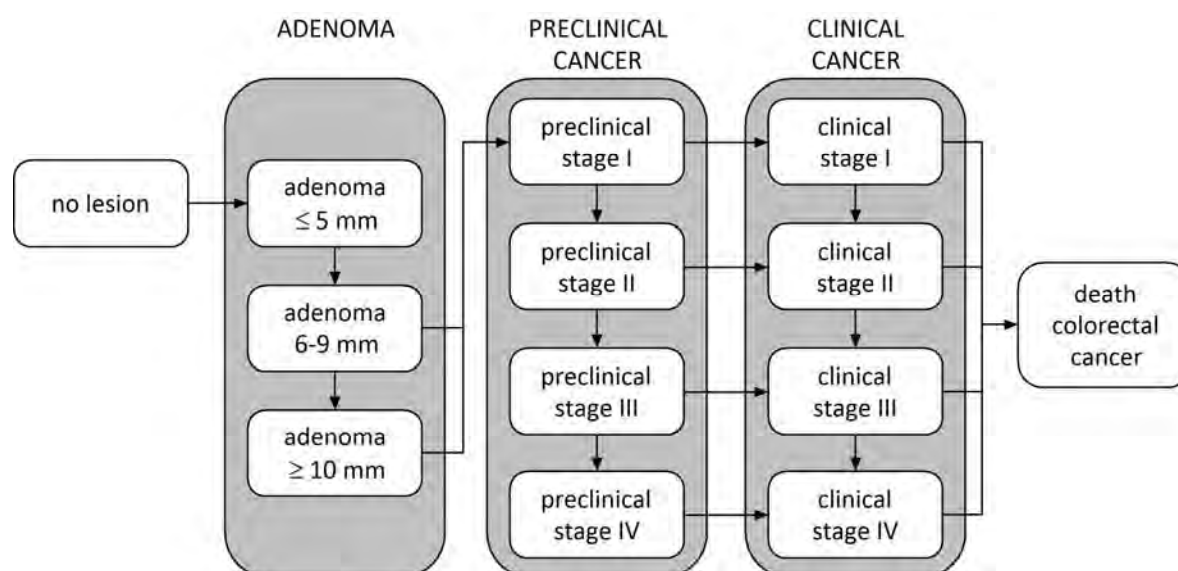
When detected in the adenoma-phase, removal of the adenoma can prevent the incidence of CRC (Winawer et al. 1993). But even when detected as an early-stage cancer, prognosis is considerably better than for late-stage cancer (Ciccolallo et al. 2005) as can be seen in Figure 1.2. Several screening tests for CRC are available, including guaiac and immunochemical faecal occult blood tests (FOBT), sigmoidoscopy, colonoscopy, CT colonography (CTC), stool DNA testing and capsule endoscopy.

1.1.3   Principles of population screening

The aim of population screening is to discover latent disease in the population in order to detect a disease in its early stages and enable it to be treated adequately before it poses a threat to the indi-

Figure 1.2: Three-year CRC survival by stage and number of lymph nodes examined, for countries in the Eurocare study (data source: Ciccolallo et al. 2005).
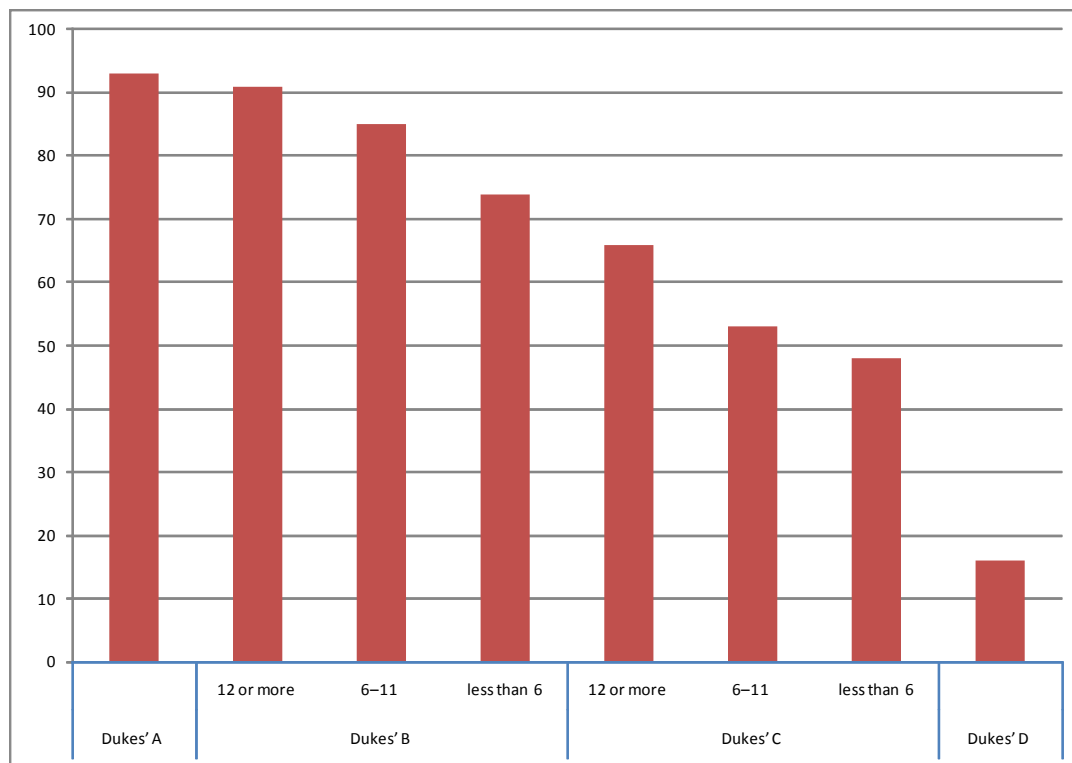
vidual and/or the community (Wilson & Jungner 1968). As such, screening is a commendable method to reduce the burden of disease. However, population screening targets an (apparently) healthy population, and should therefore only be conducted after a careful consideration of both harms and benefits.

In 1968, the World Health Organisation (WHO) defined the first set of principles for population screening (Wilson & Jungner 1968). These were:

1. The condition sought should be an important health problem for the individual and community.

2. There should be an accepted treatment or useful intervention for patients with the disease.

3. Facilities for diagnosis and treatment should be available.

4. There should be a recognisable latent or early symptomatic stage.

5. There should be a suitable screening test or examination.

6. The test should be acceptable for the population.

7. The natural history of the disease should be adequately understood.

8. There should be an agreed policy for referring for further examination and whom to treat as patients.

9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case finding should be a continuing process and not a once only project.

These principles were later extended and further elaborated for the implementation of the national screening programmes in the Netherlands (Hanselaar 2002):

1. Treatment started at an early stage should be of more benefit than treatment started later.

2. The time between test and result and between result and treatment must be as short as possible.

3. The recruitment procedure should not limit people in their freedom to participate or not in the screening programme.

4. Potential participants should receive adequate information about pros and cons of participation.

5. Benefits and risks should also be well known to healthcare providers.

6. Public education should promote a broad accessibility of the programme. It should however not include a moral pressure effect.

7. There should be quality assurance (QA) and quality control (QC) procedures for the whole screening programme.

8. Screening programmes are concerted actions meeting organisational and managerial requirements.

The above principles have been taken into account in the current EU policy on cancer screening which is laid down in the Council Recommendation on Cancer Screening of 2 December 2003 (Council of the European Union 2003) (see also Appendix 2). They show that evaluation of efficacy is a necessary condition for adopting population screening but not sufficient by itself. Many other aspects such as side effects, costs and infrastructure should also be considered. Population screening is a process that starts with educating the population about the (screening of the) disease and ends with the follow-up and treatment of patients with abnormal test results (see Sect. 1.1.4). Quality assurance and control forms a crucial aspect of this process (see Chapter 2). This introductory chapter presents the evidence which confirms that CRC screening fulfils the above criteria established by the WHO. The subsequent chapters provide comprehensive recommendations and additional applicable evidence essential to ensuring that screening programmes also fulfil the principles of best practice and quality assurance mentioned above and elucidated in the Council Recommendation on Cancer Screening (see Sect. 1.1.4).

The European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis have been developed to inform European policymakers and public health specialists, and particularly also professionals, programme managers and any other staff involved in the provision of screening services, as well as advocates, individuals in the populations invited to attend screening, and any other interested people, about the essential issues, guiding principles, standards and procedures of quality assurance and best practice which should be taken into account in running and establishing colorectal cancer screening programmes in the EU Member States. We would like to stress that these guidelines are specifically developed for screening the average-risk population for CRC. High-risk individuals should be referred for high-risk protocols if available.

1.1.4 EU policy on cancer screening

A large body of knowledge on implementation of cancer screening programmes has been acquired through the screening networks established by the European Union in the Europe Against Cancer programme which have been consolidated under the subsequent EU Health programmes in the European Cancer Network. The EU networks have shown that overall screening outcome and quality depend on the performance at each step in the screening process. To achieve the potential benefit of cancer screening, quality must therefore be optimal at every step in the process, that includes information, identification and personal invitation of the target population; performance of the screening test; and, if necessary, diagnostic work-up of screen-detected lesions, treatment, surveillance and subsequent care. Screening is performed on predominantly healthy people; comprehensive quality assurance is also required to maintain an appropriate balance between benefit and harm in the large numbers of people eligible to attend cancer screening programmes. Achieving and maintaining high quality at

every step in the screening process requires an integrated, population-based approach to health service delivery. This approach is essential in order to make screening accessible to those in the population who may benefit and in order to adequately monitor, evaluate and continuously improve performance (European Commission 1996; European Commission 2001; European Commission 2006; von Karsa et al. 2008; European Commission 2008; Perry et al. 2008; Arbyn et al. 2010).

Implementation of organised programmes is recommended because they include an administrative structure responsible for service delivery, quality assurance and evaluation. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each person in the eligible target population. Personal invitation aims to give each eligible person an equal chance of benefiting from screening and to thereby reduce health inequalities. As with evidence-based screening for breast or cervical cancer, the population-based approach to programme implementation is also recommended for CRC screening because it provides an organisational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimisation of invitation to screening and for evaluation of screening performance and impact. Nationwide implementation of population based screening programmes makes services performing to the high standards available to the entire population eligible to attend screening. Large numbers of professionals undertake further specialisation in order to meet the screening standards. Consequently, these nationwide efforts also contribute to widespread improvement in diagnosis and management of symptomatic disease (von Karsa et al. 2010).

On 2 December 2003, the Health Ministers of the European Union unanimously adopted a recommendation on cancer screening based on the developments and experience in the Europe Against Cancer programme (Council of the European Union 2003) (Appendix 2). The Recommendation of the Council of the European Union spells out fundamental principles of best practice in early detection of cancer and invites EU Member States to take common action to implement national cancer screening programmes with an organised, population-based approach and with appropriate quality assurance at all levels, taking into account European quality assurance guidelines for cancer screening, where they exist (von Karsa et al. 2008).

The adoption and subsequent implementation of the Council Recommendation on Cancer Screening has been repeatedly supported by vigorous initiatives of the European Parliament documented in parliamentary resolutions (European Parliament 2004; European Parliament 2006; European Parliament 2008). Continued, concerted efforts to implement the Council Recommendation including efforts to continuously update the European screening quality assurance guidelines have also been recommended by the Council at the conclusion of the Slovenian EU Presidency and more recently (Council of the European Union 2008; Council of the European Union 2010). These efforts, have also contributed to the adoption of the new European Partnership for Action Against Cancer which includes activities dedicated to improving implementation of the Council Recommendation (European Commission 2009).

The Council Recommendation and the EU guidelines also emphasise the need for effective communication in order to reach groups commonly found to have limited access to screening, such as less advantaged socioeconomic groups. This, in turn, should permit an informed decision about participation, based on objective, balanced information about the risks and benefits of screening (Hanselaar 2002; Giordano et al. 2006; Giordano et al. 2008; von Karsa 1995; von Karsa et al. 2010) (see also Chapter 10).

In addition to the above-mentioned fundamental principles of quality assurance in implementation of cancer screening programmes, the Council Recommendation and the European quality assurance guidelines deal with other essential elements such as registration, monitoring and training. Of particular relevance to the new European Guidelines dealing with quality assurance in colorectal cancer screening are the recommended evidence-based test for CRC and the recommended approach to introduction of novel screening tests.

The EU recommends implementation of new cancer screening tests in routine healthcare only after efficacy has been conclusively demonstrated in randomised controlled trials (RCTs) and other relevant aspects have been taken into account such as cost effectiveness in the different healthcare systems of the Member States (items 6(a) to (d) in Council Recommendation, Appendix 2). Potentially promising new modifications of established screening tests may also be considered for introduction into routine healthcare once the effectiveness of the modification has been demonstrated, possibly using other epidemiologically validated surrogate endpoints (item 6 (e) in Council Recommendation, Appendix 2).

Only the FOBT for men and women aged 50–74 years has been recommended to date by the EU for CRC screening.[2] Any change in the recommended screening policy for predominantly healthy individuals should be prepared with the utmost rigour and should be based on an evidence base appropriate to the potential impact of the decision; it should also take into account the numerous other principles and standards of best practice laid down in the Council Recommendation.

The overwhelming majority of colorectal cancer screening examinations performed in the EU use the primary screening test recommended by the Council of the European Union (FOBT). The purpose of the European Guidelines for Quality Assurance in Colorectal Cancer Screening is not to provide recommendations on which other modalities might now be suitable for CRC screening in the EU. Instead, the new European Guidelines provide guiding principles and evidence-based recommendations on the quality assurance which should be followed when implementing CRC screening using the various modalities currently adopted in publically mandated programmes in the Member States.

1.1.5   Implementation of colorectal cancer screening in Europe

Because CRC risk varies across Europe, the benefit of screening will also vary. With a high-quality screening programme and sufficient participation, the percent mortality reduction is generally expected to be similar in all countries. However, the absolute number of CRC deaths prevented depends on the background risk of CRC mortality. Therefore each country should prioritise the benefit of CRC screening against the benefit of alternative programmes. Nevertheless, the levels of CRC incidence throughout Europe indicate that the potential benefit of CRC screening is significant in all European countries.

By the end of 2007, several EU Member States were in the process of implementing a national population screening programme (von Karsa et al. 2008; Commission of the European Communities 2008) (see Appendix 3). Population-based programmes were being rolled out nationwide in five countries (Finland, France, Italy, Poland and the United Kingdom). Furthermore, seven countries had established nationwide non-population-based programmes (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia and the Slovak Republic). Another five countries were planning or piloting a nationwide population-based programme (Hungary, Cyprus, Portugal, Romania and Slovenia). Of these 17 countries, ten had adopted only FOBT, six used both FOBT and endoscopy and one only colonoscopy. In the meantime, ten Member States have established or upgraded the status of their CRC screening programmes (Czech Republic, France, Ireland, Lithuania, Portugal, Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom). In addition Denmark and the Netherlands are currently in the decision process for implementing a CRC screening programme.

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[2] Other evidence-based screening tests currently recommended by the Council of the European Union: pap smear screening (cervical cytology) for cervical cancer precursors starting not before the age of 20 and not later than the age of 30 years in accordance with European guidelines for quality assurance in cervical cancer screening (Council Recommendation 1(b)); mammography screening for breast cancer in women aged 50 to 69 years in accordance with European guidelines for quality assurance in breast cancer screening and diagnosis (Council Recommendation 1(b)).

As mentioned above, the current EU screening policy only recommends faecal occult blood testing for population-based screening (Council of the European Union 2003) (see Section 1.1.4). Currently, the guaiac FOBT is the only test for which extensive evidence of efficacy has been established in more than one RCT (Hardcastle et al. 1996; Kronborg et al. 1996; Mandel et al. 1999; Lindholm, Brevinge & Haglind 2008).

1.2 Evidence for effectiveness of FOBT screening

With FOBT, stool samples are analysed for the presence of occult blood. FOBTs are either guaiac-based (gFOBT) or immunochemical tests (iFOBT). GFOBTs investigate the presence of any blood, whereas iFOBTs are specific for human blood (for more detailed information on test characteristics and clinical performance, see Chapter 4).

1.2.1 Guaiac FOBT[3]

1.2.1.1 Evidence for efficacy

Three systematic reviews have evaluated the evidence for the efficacy of gFOBT screening (Heresbach et al. 2006; Hewitson et al. 2007; Kerr et al. 2007). The reviews all included the RCTs of Minnesota, Nottingham and Funen which compare gFOBT screening with no screening (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996). In addition, the Cochrane review by Hewitson also included the then-unpublished results of the Goteborg study (Lindholm, Brevinge & Haglind 2008), whereas the Heresbach review also included the block-randomised trial from Burgundy (Faivre et al. 2004). All three reviews found a significant reduction in CRC mortality: the relative risk of dying from CRC in the screening arm compared to the control arm varies from 0.84–0.86, implying a 14–16% reduction in CRC mortality. GFOBT screening was not found to have an effect on overall mortality (Hewitson et al. 2007).

In a subgroup analysis, Heresbach showed that CRC mortality reduction was confined to the first 10 years of screening (six rounds) and that CRC mortality was not decreased during the 5–7 years after that, nor in the second phase (8–16 years after the onset of screening) of the Minnesota screening trial (Heresbach et al. 2006).

In conclusion, there is good evidence that gFOBT screening reduces CRC mortality by 14%–16% in people of appropriate age invited to attend screening. The observed, modest reduction in CRC mortality has not been shown to impact overall mortality **(I).**[Rec 1.1]

1.2.1.2 Evidence for the interval

There are no specific trials investigating the best screening interval for programmes with gFOBT. One RCT conducted in the Minnesota area on healthy volunteers aged 50 to 80 years reported data on annual and biennial screening (Mandel et al. 1993). After 13 years of follow-up, a statistically significant

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[3] gFOBT is an evidence-based screening test for CRC recommended by the EU. The applicable item in the Council Recommendation of 2 December 2003 is 1(a) (see Sect. 1.14 and Appendix 2).

33% CRC mortality reduction was reported in the annual screening group compared to the control group. At that time, biennial screening resulted in a non-significant 6% mortality reduction. Two European trials (in England and in Denmark) subsequently showed statistically significant 15% and 18% mortality reductions, respectively, with biennial screening (Hardcastle et al. 1996; Kronborg et al. 1996). A second publication of the Minnesota trial provided updated results through 18 years of follow-up and reported a 21% CRC mortality reduction in the biennial screening group, while the reduction in CRC mortality for annual screening remained 33% (Mandel et al. 1999).

In conclusion, both annual and biennial screening with gFOBT have been shown to be effective methods for significantly reducing CRC mortality **(I)**. The results of the Minnesota trial imply that the benefit from annual screening appears to be greater than for biennial screening **(II)**. No clear recommendation regarding the best time interval for offering screening by gFOBT can be drawn. To ensure effectiveness, the screening interval in a national screening programme should not exceed two years **(II - B)**.[Rec 1.2]

1.2.1.3 Evidence for the age range

There are no specific trials investigating the optimal age range for gFOBT screening. None of the RCTs investigating annual or biennial screening by gFOBT reported a formal subgroup analysis regarding efficacy of screening in different age groups (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996; Lindholm, Brevinge & Haglind 2008). Data from the Nottingham trial at 11 years of follow up showed no difference in CRC mortality rates between subjects older and younger than 65 years (Scholefield et al. 2002).

Circumstantial evidence for the age range comes from the differences in age range of the RCTs. Table 1.2 gives an overview of the age ranges of the four RCTs of Minnesota, Nottingham, Funen and Goteborg and the observed mortality reductions in these trials (Hewitson et al. 2007). Goteborg investigated the narrowest age range from age 60 to 64, whereas the other trials have included individuals as young as 45 and as old as 80. Considering the limit of this indirect comparison, the table shows that CRC mortality reduction is significant for all age ranges and that the magnitude of the relative risk reduction is similar for all age ranges investigated.

Table 1.2: **Age range and mortality reduction in the four randomised controlled trials on FOBT**

Study	Age range	RRR CRC mortality	Years of follow-up
Nottingham	45–75	13% (CI 0.78–0.97)	11 years
Funen	45–74	11% (CI 0.78–1.01)	17 years
Minnesota	50–80	21% (CI 0.62–0.97)	18 years
Goteborg	60–64	16% (CI 0.78–0.90)	15.5 years

RRR: Relative risk reduction

In summary, the best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years **(IV)**. The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources **(VI - B)**.[Rec 1.3]

1.2.1.4 Evidence on risks vs. benefit and cost-effectiveness

GFOBT screening is a safe screening method with no direct adverse health effects. However, it is associated with false-positive test results, leading to anxiety and unnecessary follow-up colonoscopies. Approximately 1% of screened individuals in the Nottingham and Funen trials had a positive gFOBT and no adenomas or CRC detected at follow-up colonoscopy. In the UK pilot programme of gFOBT screening, a similar false positivity rate was found. Because of rehydration of the gFOBT, the rate of false-positive test results was almost 9% in the Minnesota trial.

Per 10 000 follow-up colonoscopies after positive tests, approximately 7 perforations and 9 major bleeds were reported in the RCTs of Nottingham and Minnesota. In the UK pilot programme 5 perforations per 10,000 colonoscopies were reported. For unrehydrated gFOBT, this means that there are approximately 16 major complications from unnecessary colonoscopies per 1 million persons screened. For rehydrated gFOBT these values are almost 10 times as high. No colonoscopy-related deaths were reported in any of the RCTs, or in the UK pilot programme.

In a well-organised, high-quality screening programme using unrehydrated gFOBT, the risks of adverse effects are limited **(I)**.

A systematic review (Pignone et al. 2002a) for the United States Preventive Services Task Force (USPSTF) compared the cost-effectiveness of the following CRC screening strategies: FOBT; sigmoidoscopy; the combination of FOBT and sigmoidoscopy; and colonoscopy. The included studies found that the cost-effectiveness of CRC screening with annual or biennial gFOBT varied from US$ 5 691 to US$ 17 805 per life-year gained (Pignone et al. 2002a). The included studies differed with respect to what screening strategies were most cost-effective and the review concluded that no recommendation of one screening strategy over the others could be made based on the available evidence **(III - D).** Rec 1.17

Two studies specifically investigated the cost-effectiveness of gFOBT screening in Europe (Lejeune et al. 2004; Whynes 2004). The first one estimated the cost-effectiveness of biennial FOBT screening over up to five screening rounds within the Nottingham trial (Whynes 2004). The cost of screening was US$ 8 300 (£ 5 290) per cancer detected (at 2002 prices). Under conservative assumptions, the incremental cost per life year gained as a result of screening was US$ 2 500 (£ 1 584). A French cost-effectiveness analysis on a hypothetical cohort of 100 000 asymptomatic individuals aged 50 to 74 years confirmed that biennial FOBT screening for CRC was a cost-effective strategy (Lejeune et al. 2004). Incremental costs per life-year gained of screening over no screening were US$ 4 600 (€ 3 375) and US$ 6 400 (€ 4 705) with a 20 and 10-year time horizon, respectively.

Costs per life-year gained with gFOBT screening are well below the commonly used cost-effectiveness threshold of US$ 50 000 per life-year gained **(III).**Rec 1.15

1.2.2 Immunochemical FOBT[4]

1.2.2.1 Evidence for efficacy

To date, there has been one RCT evaluating the efficacy of iFOBT screening. In this study, 94 423 individuals were offered a once-only iFOBT screen. After 8 years, the investigators found a statistically significant 32% reduction in rectal cancer mortality, but no reduction in colonic or overall CRC mortal-

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[4] iFOBT is an evidence-based screening test for CRC that fulfils the requirements of the Council Recommendation of 2 December 2003. The applicable items in the Recommendation are 1(a) in combination with 6(e) (see Sect. 1.14 and Appendix 2).

ity (Zheng et al. 2003). There are two caveats concerning this study: Firstly, follow-up of positive iFOBT was performed by flexible sigmoidoscopy, which may explain the lack of effectiveness in the entire colon. Furthermore, randomisation was based on townships and not on individuals.

In addition, three Japanese case–control studies evaluated the efficacy of iFOBT (Saito et al. 1995; Saito et al. 2000; Nakajima et al. 2003). All three studies found a significant reduction in CRC mortality from iFOBT screening, ranging from 23% to 81%, depending on the study and years since last iFOBT.

Clinical societies have argued that it might be appropriate to implement a new CRC screening test without an RCT on CRC mortality, if there is convincing evidence that the new test has: (1) at least comparable performance (e.g. sensitivity and specificity) in detecting cancers and adenomas; (2) is equally acceptable to patients and (3) has comparable or lower complication rates and costs (Winawer et al. 1997). This evidence is available for iFOBT: there have been 13 population-based screening studies comparing performance characteristics of gFOBT and iFOBT (Allison et al. 1996; Castiglione et al. 1996; Rozen, Knaani & Samuel 2000; Zappa et al. 2001; Ko, Dominitz & Nguyen 2003; Wong et al. 2003; Hughes et al. 2005; Hoepffner et al. 2006; Smith et al. 2006; Allison et al. 2007; Guittet et al. 2007; Dancourt et al. 2008; van Rossum et al. 2008). Although the studies used different tests and slightly different protocols, the results of all studies consistently showed that iFOBT has significantly higher sensitivity for advanced adenomas and cancer than the gFOBT (Hemoccult II). For some cut-off levels for referral, iFOBT was also more specific (see also Ch. 4, Sect. 4.2.5 and 4.3.2).

There is reasonable evidence from an RCT **(II)** that iFOBT screening reduces rectal cancer mortality, and from case control studies **(IV)** that it reduces overall CRC mortality. There is additional evidence showing that iFOBT is superior to gFOBT with respect to detection rate and positive predictive value **(III)**.[Rec 1.4]

1.2.2.2 Evidence for the interval

The three case–control studies evaluating the efficacy of iFOBT showed that a reduction in risk of CRC death was only statistically significant for those subjects screened within three years prior to the diagnosis. No reduction in risk was observed after three years.

This circumstantial evidence suggests that the screening interval with iFOBT should not exceed three years **(III)**. Due to lack of additional evidence, the interval for iFOBT screening can best be set at that for gFOBT, but should not exceed three years **(VI - C)**.[Rec 1.5]

1.2.2.3 Evidence for the age range

No evidence is available on the best age range for iFOBT screening. Given the similarities between the tests, the age range for a screening programme using iFOBT can best be based on the limited evidence for the optimal age range from gFOBT trials (see Rec. 1.3, Sect. 1.2.1.3) **(VI - C)**.[Rec 1.6]

1.2.2.4 Evidence on risks vs. benefit and cost-effectiveness

As with gFOBT, there are no serious adverse health effects directly attributable to iFOBT screening. Complications in an iFOBT screening programme occur from diagnostic colonoscopies after positive test results. Approximately 2–3% of individuals offered iFOBT screening in the Italian SCORE 2 and 3 trials (Segnan et al. 2005; Segnan et al. 2007) and in the NORCCAP trial (Gondal et al. 2003) had a positive iFOBT without adenomas or CRC detected at subsequent diagnostic colonoscopy. In the NORCCAP study, six perforations were reported after colonoscopy (Gondal et al. 2003). However, all of these complications occurred in therapeutic colonoscopies following polypectomy. There were no

perforations in purely diagnostic colonoscopies without adenomas or cancer detected. In addition, there were four major bleeds and one burnt serosa syndrome. The total complication rate with colonoscopy was 4 per 1 000 colonoscopies (Gondal et al. 2003).

In a well-organised high-quality iFOBT screening programme, the risks of adverse effects are limited **(III)**.

There were no studies specifically addressing the cost-effectiveness of iFOBT, but three studies that compared the cost-effectiveness of iFOBT to that of gFOBT (Berchi et al. 2004; Li et al. 2006; Parekh, Fendrick & Ladabaum 2008). Two studies concluded that iFOBT screening was at least as effective as gFOBT screening, but less costly (Li et al. 2006; Parekh, Fendrick & Ladabaum 2008). In the third analysis, the use of iFOBT for 20 years of biennial screening cost € 59 more than gFOBT per target individual, and led to a mean increase in individual life expectancy of 0.0198 years, which corresponds to an incremental cost-effectiveness ratio of US$ 4 100 (€ 2 980) per years of life saved.

In conclusion, iFOBT seems to be a cost-effective alternative to gFOBT, either dominating gFOBT or providing incremental benefit at costs per life-year gained well below the commonly used threshold of US$ 50 000 per life-year gained **(III).**[Rec 1.15; 1.16]

1.3 Evidence for effectiveness of endoscopy screening

With endoscopy screening, a flexible tube is inserted into the anus to inspect the colorectum. With this procedure, the physician can detect abnormalities and remove them in one procedure. The two main endoscopy procedures are flexible sigmoidoscopy and colonoscopy. With sigmoidoscopy only approximately one-half of the colorectum can be inspected, whereas colonoscopy generally visualises the complete colorectum.

1.3.1 Sigmoidoscopy[5]

1.3.1.1 Evidence for efficacy

For sigmoidoscopy screening, evidence on the efficacy is available from three RCTs: the Telemark and NORCCAP studies in Norway and the large UK study in which 57 237 individuals were randomised to the screening group for once-only sigmoidoscopy alone (Table 1.3). The UK study was the only study to find a significant 31% reduction in CRC mortality from sigmoidoscopy in an intention-to-treat analysis (Atkin et al. 2010). However, the Norwegian trials had considerably smaller sample sizes (13,823 individuals in the screening group in the NORCCAP study, and only 400 in the Telemark study); the NORCCAP study also had a shorter follow-up. Therefore these studies may have been underpowered (Thiis-Evensen et al. 1999; Hoff et al. 2009). In per-protocol analyses, the NORCCAP study did find a significant reduction in CRC mortality. Both the Telemark and UK study found a significant reduction in CRC incidence. The disturbing finding in the very small Telemark study that sigmoidoscopy screening

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[5] Flexible sigmoidoscopy is not a screening test for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and Appendix 2).

might increase overall mortality in the screening group was not corroborated by either the NORCCAP or UK study. The UK trial used a two-step invitation process in which only people who actively expressed their interest in being randomised were enrolled. Although CRC incidence in the trial control group was similar to what is expected in the general population, the results cannot be directly extrapolated to the general population. Future results from 2 other large RCTs in Italy and the US will be used to assess the findings of these trials (Prorok et al. 2000; Segnan et al. 2002).

Table 1.3: CRC Incidence and mortality reduction from three randomised controlled trials on sigmoidoscopy screening

Outcome	Telemark, Norway	NORCCAP, Norway	UK FS trial, UK
Intention-to-treat analysis			
CRC incidence	80% reduction*	No difference	23% reduction*
CRC mortality	50% reduction	27% reduction	31% reduction*
Overall mortality	57% increase*	No difference	No difference
Per-protocol analysis			
CRC incidence	-	-	33% reduction*
CRC mortality	-	59% reduction*	43% reduction*

* significant   -   not reported

In addition, three case-control studies of good methodological quality have been published. In these studies, sigmoidoscopy was compared with no screening (Newcomb et al. 1992; Selby et al. 1992; Muller & Sonnenberg 1995) while adjusting for the main confounding factors (family history of CRC, FAP, polyposis, ulcerative colitis and number of periodic health examinations). All three studies found a significant reduction in CRC mortality and two of them also in CRC incidence. Finally, a prospective cohort study including 24 744 asymptomatic men aged 40–75 years at average risk of CRC, showed a significant 42% reduction in overall CRC incidence and 56% in distal cancer incidence from screening endoscopy after 8 years of follow-up. The study did not find a significant difference in proximal cancer incidence or overall CRC mortality (Kavanagh et al. 1998).

In conclusion, there is reasonable evidence that flexible sigmoidoscopy screening reduces CRC incidence and mortality, if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs **(II).**[Rec 1.7]

1.3.1.2 Evidence for the interval

There are no studies directly assessing the optimal interval for sigmoidoscopy screening. Two studies have evaluated the detection rate of adenomas and cancer three and five years, respectively, after a negative sigmoidoscopy (Platell, Philpott & Olynyk 2002; Schoen et al. 2003). Both studies found a significantly lower detection rate at the second screening than at initial screening. The rates were 65%–75% lower three years after a negative examination, (Schoen et al. 2003) and 50% lower 5 years after a negative examination (Platell, Philpott & Olynyk 2002). Nevertheless, the authors of the two studies arrived at different conclusions: Platell suggested that rescreening the average-risk population with flexible sigmoidoscopy at intervals longer than 5 years could be considered, whereas Schoen concluded that although the overall percentage of detected abnormalities is modest, the data raise concern about the impact of a screen interval longer than 3 years after a negative examination. The UK flexible sigmoidoscopy screening study showed that there was little attenuation of the protective effect of sigmoidoscopy after 11 years of follow-up (Atkin et al. 2010), suggesting that the inter-

val for rescreening should not be less than 10 years. This is in line with the evidence for colonoscopy screening (see Sect. 1.3.2.2).

In conclusion, the optimal interval for sigmoidoscopy screening was only assessed in two indirect studies that only considered intervals of three and five years. The UK flexible sigmoidoscopy study and evidence for colonoscopy screening seems to indicate that the optimal interval for endoscopy screening should not be less than 10 years and may even be extended to 20 years (see Sect. 1.3.2.2)

1.3.1.3 Evidence for the age range

Evidence on the age-specific prevalence of colorectal adenomas suggests that the best age range for flexible sigmoidoscopy screening is between 55 and 64 (Segnan et al. 2007). A significant reduction in incidence and mortality of CRC has recently been shown in this age range in a large RCT using flexible sigmoidoscopy performed once in a lifetime as the primary screening test (Atkin et al. 2010).

There has been one cross-sectional study comparing safety, tolerability, completion, and endoscopic findings of sigmoidoscopy between individuals 50–74 years old and individuals 75 years and older (Pabby et al. 2005). The study demonstrated that elderly subjects ≥75 years old have an increased rate of endoscopist-reported difficulties and a higher rate of incomplete examinations compared to subjects aged 50–74 years. Complication rate and detection rate of adenomas and advanced adenomas were similar in both cohorts, while an increased detection of carcinomas in the elderly was observed.

In conclusion, there is limited evidence suggesting that the best age range for flexible sigmoidoscopy screening should be between 55 and 64 years **(III – C).** One study suggests that for screening in the elderly population (75 years and older) tolerability is an issue **(V)**. Average-risk sigmoidoscopy screening should be discontinued after age 74, given the increasing co-morbidity in this age range **(V - D).**[Rec 1.9.]

1.3.1.4 Evidence on risks vs. benefit and cost-effectiveness

Four population-based screening trials reported on complication rates with flexible sigmoidoscopy (Table 1.4). Severe complication rates from sigmoidoscopy varied from 0% to 0.03%. Minor complications occurred in 0.2–0.6% of sigmoidoscopies. Severe complication rates with follow-up colonoscopy were about 10 times as high as with sigmoidoscopy (0.3%–0.5%). Minor complications occurred in 1.6%–3.9% of follow-up colonoscopies.

In a well-organised high-quality flexible sigmoidoscopy screening programme the risk of severe complications is about 0%–0.03% for sigmoidoscopies and 0.3%–0.5% for follow-up colonoscopies **(III).**

Six studies in the USPSTF review estimated the cost-effectiveness of sigmoidoscopy screening, (Pignone et al. 2002a). One study showed that with favourable conditions sigmoidoscopy screening could be cost-saving. In the other studies the cost-effectiveness ratio varied from US$ 12 477 to US$ 39 359 per life-year gained. More recent cost-effectiveness analyses found similar ratios (US$ 7 407– US$ 23 830) (Song, Fendrick & Ladabaum 2004; Pickhardt et al. 2007; Vijan et al. 2007). A recent study based in England also estimated that sigmoidoscopy screening could be cost-saving (Tappenden et al. 2007).

All cost-effectiveness analyses show that the cost-effectiveness of sigmoidoscopy screening is below the commonly used threshold of US$ 50 000 per life-year gained. Some studies suggest that sigmoidoscopy screening could even be cost-saving **(III).**[Rec 1.15]

Table 1.4: Major and minor complication rates in population-based sigmoidoscopy screening

	SCORE (Segnan et al. 2002)	SCORE 2 (Segnan et al. 2005)	UK FS trial (UK Flexible Sigmoidoscopy Screening Trial Investigators 2002)	NORCCAP (Gondal et al. 2003)
Sigmoidoscopy				
Severe complications	0.02%	0.02%	0.03%	0%
Minor complications	0.6%	0.5%	0.2%	0.2%
FU colonoscopy				
Severe complications	0.3%	0.3%	0.5%	0.4%
Minor complications	3.9%	3.9%	0.4%	1.6%

1.3.2 Colonoscopy[6]

1.3.2.1 Evidence for efficacy

Until recently, there has been no RCT investigating the efficacy of colonoscopy screening; a large multicentre trial is currently underway in Norway, Poland, the Netherlands, Iceland, Sweden and Latvia comparing the efficacy of a once-only colonoscopy to no screening. Systematic reviews evaluating the efficacy of colonoscopy screening (Pignone et al. 2002b; Walsh & Terdiman 2003) include one prospective observational study comparing CRC incidence in a population that underwent colonoscopy and removal of detected lesions with the incidence of three reference populations (Winawer et al. 1993). Incidence in the cohort under investigation was 76% to 90% lower than that of the reference populations. These results should be interpreted with caution because the study used historical controls that were not from the same underlying population. Recently, a second prospective observational study showed a 65% lower CRC mortality and 67% lower CRC incidence in individuals with a screening colonoscopy compared to the general population (Kahi et al. 2009). Two recent case–control studies also found a significant reduction of 31% in CRC mortality (Baxter et al. 2009) and 48% in advanced neoplasia detection rates (Brenner et al. 2010). However, the reduction in these studies was limited to the rectum and left side of the colon. No significant reduction was found in right-sided disease.

Cross-sectional surveys have shown that colonoscopy is more sensitive than sigmoidoscopy in detecting adenomas and cancers and that this increased sensitivity could translate into increased effectiveness (Walsh & Terdiman 2003).

In conclusion, limited evidence exists on the efficacy of colonoscopy screening on CRC incidence and mortality **(III)**. However, recent studies suggest that colonoscopy might not be as effective in the right colon as in other segments of the colorectum **(IV)**.[Rec 1.10] Results of at least one large RCT would permit more definitive conclusions about the efficacy of colonoscopy as a primary screening test.

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[6] Colonoscopy is not a screening test for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and Appendix 2).

1.3.2.2 Evidence for the interval

The optimal interval for colonoscopy screening has been assessed in a cohort study and a case-control study. The cohort study found that CRC incidence in a population with negative colonoscopy was 31% lower than general population rates and remained reduced beyond 10 years after the negative colonoscopy (Singh et al. 2006). Similar results were obtained in the case–control study (Brenner et al. 2006): after adjustment for potential confounding variables, a previous negative colonoscopy was associated with a 74% lower risk of CRC. This risk reduction persisted up to 20 years. Several prospective studies found a risk of adenoma 5 years after a negative colonoscopy ranging from 2.1% to 2.7% and a risk of advanced adenoma or cancer ranging from 0.0% to 2.4% (Rex et al. 1996; Huang et al. 2001; Ee, Semmens & Hoffman 2002; Yamaji et al. 2004; Lieberman et al. 2007).

Evidence for the timing of colonoscopy intervals is limited. A cohort and case-control study suggest that screening colonoscopies do not need to be performed at intervals shorter than 10 years and that this time interval may even be extended to 20 years **(III - C).**[Rec 1.11]

1.3.2.3 Evidence for the age range

Evidence on the age-specific prevalence of colorectal adenomas suggests that the best age range for colonoscopy screening is between 55 and 64 (Segnan et al. 2007). However, no studies have been published which directly investigated the optimal age range for colonoscopy screening. Two cross-sectional studies compared detection rates in a cohort of 40-49-year-olds with those in older cohorts (Imperiale et al. 2002; Rundle et al. 2008). Although an increase in the prevalence of neoplasms in the 50–59 years age group compared with the 40–49 years age group was observed in the first study, this difference was not statistically significant (Rundle et al. 2008). The prevalence of CRC in the second study was significantly lower in the 40–49-year-old cohort than in the cohort older than 49 years (p=0.03), (Imperiale et al. 2002). A German case–control analysis assessed the possible impact of colonoscopic screening history in different age groups (Brenner et al. 2005). For all screening schemes except those with a single endoscopy around age 50 or 70, strong, highly significant risk reductions between 70% and 80% were estimated. The optimal age for a single screening endoscopy appeared to be around 55 years. The previously reported cross-sectional study on safety, tolerability, completion, and endoscopic findings of sigmoidoscopy screening (see Sect. 1.3.1.3) suggests that tolerability is also an issue in colonoscopy screening in individuals over 74 years of age (Pabby et al. 2005).

There is no direct evidence confirming the optimal age range for colonoscopy screening. Indirect evidence suggests that the prevalence of neoplastic lesions in the younger population (less than 50 years) is too low to justify colonoscopic screening, while in the elderly population (≥75 years) lack of benefit could be a major issue. The optimal age for a single colonoscopy appears to be around 55 years **(IV - C).** Average risk colonoscopy screening should not be performed before age 50 and should be discontinued after age 74 **(V - D).**[Rec 1.12]

1.3.2.4 Evidence on risks vs. benefit and cost-effectiveness

Major complication rates with screening colonoscopy were obtained from five population-based studies and varied from 0–0.3% (Table 1.5) (Lieberman et al. 2000; Schoenfeld et al. 2005; Regula et al. 2006; Kim et al. 2007; Rainis et al. 2007). None of the studies reported minor complications. Complication rates with screening colonoscopies are considerably higher than for sigmoidoscopy, but slightly lower than for follow-up colonoscopies after a positive FOBT or sigmoidoscopy. The balance between benefit and harm for people attending screening colonoscopy may still be less favourable than for people attending FOBT screening, because relatively few people in the FOBT target population are exposed to the potential harm of follow-up colonoscopy.

In a well-organised high-quality colonoscopy screening programme, major complications occur in 0-0.3% of colonoscopies. **(IV)**

Six studies in the USPSTF review estimated the cost-effectiveness of colonoscopy screening. The cost-effectiveness of colonoscopy screening varied in these studies from US$ 9 038 to US$ 22 012 per life-year gained. Recent studies found similar ratios (US$ 8 090–US$ 20 172) (Ladabaum et al. 2001; Song, Fendrick & Ladabaum 2004; Pickhardt et al. 2007; Vijan et al. 2007). One recent study in Germany estimated that a once-only colonoscopy screening could be cost-saving compared to no screening (Sieg & Brenner 2007).

All cost-effectiveness analyses show that the cost-effectiveness of colonoscopy screening is below the commonly used threshold of US$ 50 000 per life-year gained **(III)**.[Rec 1.15]

Table 1.5: Complication rates with screening colonoscopies

	Lieberman et al. 2000	Regula et al. 2006	Schoenfeld et al. 2005	Rainis et al. 2007	Kim et al. 2007
Severe complications	0.3%	0.1%	0%	0.08%	0%

1.4 Evidence for effectiveness of FOBT and sigmoidoscopy combined[7]

No trials have assessed the impact of combining sigmoidoscopy screening with annual or biennial FOBT on CRC incidence or mortality. One trial comparing a combination of flexible sigmoidoscopy and once-only FOBT with sigmoidoscopy alone did not find a lower post-screening CRC incidence in the group with the combination strategy than in the group with sigmoidoscopy alone (Hoff et al. 2009).

Four studies reported diagnostic yield with a combination of once-only sigmoidoscopy and once-only FOBT, compared to FOBT and/or sigmoidoscopy alone (Rasmussen et al. 1999; Lieberman & Weiss 2001; Gondal et al. 2003; Rasmussen, Fenger & Kronborg 2003; Segnan et al. 2005). The yield of the combination of once-only sigmoidoscopy with once-only FOBT was significantly higher than that of once-only FOBT alone, but not higher than that of once-only sigmoidoscopy alone.

When a once-only combination of sigmoidoscopy with FOBT was compared with biennial FOBT alone, the cumulative detection rates for cancer and advanced adenoma became similar among the two strategies after 5 rounds of biennial FOBT screening (Rasmussen, Fenger & Kronborg 2003). When the detection rate was calculated among the invited (as opposed to examinees) diagnostic yield was higher in the biennial FOBT programme because of the higher compliance with FOBT. These conclusions should be considered cautiously, however, because they are based on an indirect comparison of two trials and because sigmoidoscopy may prevent advanced adenomas and CRC. A comparison of cumulative detection rates of advanced adenomas and CRC may therefore be biased in favour of biennial FOBT screening.

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[7] Combination of FOBT and sigmoidoscopy is not a screening approach for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and Appendix 2).

Two studies evaluated the effect of offering combined once-in-a-lifetime testing on screening compliance (Gondal et al. 2003; Segnan et al. 2005). While one study showed a significantly lower compliance with the combination of sigmoidoscopy and FOBT compared to FOBT alone (Segnan et al. 2005) the other did not find a difference between the combination, and sigmoidoscopy alone (Gondal et al. 2003).

The impact on CRC incidence and mortality of combining sigmoidoscopy screening with annual or biennial FOBT has not yet been evaluated in trials. There is currently no evidence for extra benefit from adding a once-only FOBT to sigmoidoscopy screening **(II)**.[Rec 1.13]

1.5 New screening technologies under evaluation[8]

Besides the established FOBT and endoscopy tests, several new technologies are currently under development for CRC screening. The most important ones are CT colonography (CTC), stool DNA and capsule endoscopy screening. There currently is no evidence on the effect of these and other new screening tests under evaluation on CRC incidence and mortality (see Sections 1.5.1–3) New screening technologies are therefore not recommended for screening the average-risk population **(VI - D).**
[Rec 1.14]

1.5.1 CT colonography

CTC is a potential technique for CRC screening. With CTC, two- and three-dimensional digital images are constructed to investigate the presence of lesions in the colon and rectum. Studies on the impact of CTC screening on CRC incidence or mortality have not yet been conducted. Seven systematic reviews have been published between 2003 and 2008 on CTC performance characteristics in comparison to colonoscopy (Sosna et al. 2003; Halligan et al. 2005; Mulhall, Veerappan & Jackson 2005; Purkayastha et al. 2007; Rosman & Korsten 2007; Walleser et al. 2007; Whitlock et al. 2008). All meta-analyses and primary studies (Reuterskiold et al. 2006; Arnesen et al. 2007; Chaparro Sanchez et al. 2007) reported that sensitivity was low for small polyps and increased with polyp size. The incidence of adverse events was very low in all studies which assessed this outcome. Three studies also reported patient preferences and found that participants prefer CT colonography over colonoscopy, (Jensch et al. 2008; Roberts-Thomson et al. 2008). None of the retrieved studies considered the possible damage associated with radiation. All studies concluded that CT is not ready for routine use in clinical practice.

Before CTC can be recommended for average-risk screening, it must be demonstrated to be highly and consistently sensitive in a variety of settings and questions about the optimal technological characteristics of the technique must be settled. These questions include the appropriate threshold size for referral of findings, costs of the procedure in relation to its effectiveness and the potential risks from the radiation exposure **(VI - A).**

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[8] New technologies under evaluation are not recommended for CRC screening by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and Appendix 2).

1.5.2 Stool DNA

With stool DNA testing, faeces are investigated for the presence of disrupted or methylated DNA. There have been no studies evaluating the CRC incidence or mortality reduction from stool DNA testing. Systematic reviews of performance characteristics of stool DNA tests (Bluecross Blueshield Association Special Report: 2006; Whitlock et al. 2008; Loganayagam 2008) included two prospective studies assessing diagnostic performance in an average-risk population (Imperiale et al. 2004; Ahlquist et al. 2005). Both studies found that stool DNA testing was more sensitive than Hemoccult II for advanced neoplasia, without loss of specificity. However, sensitivity of stool DNA was still only 50% and 20% in the respective studies (Imperiale et al. 2004; Ahlquist et al. 2005).

A new version of the stool DNA test has been developed that incorporates only two markers. The use of only two markers will make the test easier to perform, reduce the cost, and facilitate distribution to local laboratories. In a case–control study of this test, Itzkowitz found a high sensitivity of 83% but the specificity was significantly worse than the older version at 82% (Itzkowitz et al. 2008).

An important issue which must be addressed before widespread implementation of stool DNA testing becomes possible involves costs. Two studies have shown that at current costs of approximately US$ 350, stool DNA screening is not a cost-effective option for CRC screening (Zauber et al. 2007; Parekh, Fendrick & Ladabaum 2008). According to one study, costs should be 6–10 times lower before stool DNA screening could compete with other available screening tests (Zauber et al. 2007).

Stool DNA with version 1 testing has superior sensitivity over Hemoccult II, at similar levels of specificity **(III)**. Version 2 seems to have even better sensitivity, at the expense of worse specificity **(IV)**. The diagnostic accuracy of stool DNA needs to be confirmed by large multicentre prospective trials in the average-risk population, and costs need to be reduced before stool DNA testing can be recommended for CRC screening **(VI - D).**

1.5.3 Capsule endoscopy

With capsule endoscopy, a camera with the size and shape of a pill is swallowed to visualise the gastrointestinal tract. No studies have reported on CRC incidence and mortality reduction from capsule endoscopy. Two reviews have evaluated its test performance characteristics compared to colonoscopy and/or CT colonography (Fireman & Kopelman 2007; Tran 2007). Since the reviews, four more studies on the diagnostic accuracy of capsule endoscopy have been published (Eliakim et al. 2009; Gay et al. 2009; Sieg, Friedrich & Sieg 2009; Van Gossum et al. 2009). Sensitivity in the studies included in the review varied from 56–76%, and specificity from 64–69% (Fireman & Kopelman 2007; Tran 2007). The newer studies showed somewhat better estimates than the earlier studies, with sensitivity ranging from 72–78% and specificity from 53–78% (Eliakim et al. 2009; Gay et al. 2009; Sieg, Friedrich & Sieg 2009; Van Gossum et al. 2009). However, these test characteristics are still inferior compared to colonoscopy.

Capsule endoscopy bears promise as an alternative to colonoscopy, because the examination can be realised without intubation, insufflation, pain, sedation or radiation; no serious adverse effects have been reported. However, accuracy data show inferior performance compared to colonoscopy **(III)**. Better diagnostic performance results from large multicentre prospective trials in the average-risk population are required before capsule endoscopy can be recommended for screening **(VI - A).**[Rec 1.14]

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

2
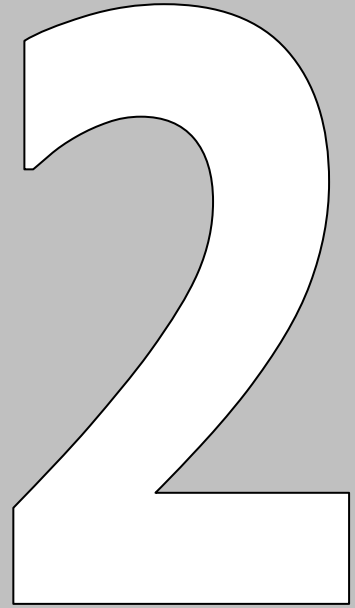
Organisation

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Guiding principles for organising a colorectal cancer screening programme

1. A colorectal cancer screening programme is a multidisciplinary undertaking. The objective is to reduce mortality from and possibly incidence of colorectal cancer without adversely affecting the health status of those who participate in screening. The effectiveness is a function of the quality of the individual components of the process.

2. The provision of the service must account for the values and preferences of individuals as well as the perspectives of public health.

3. The public health perspective in the planning and provision of screening services requires commitment to ensuring equity of access and sustainability of the programme over time.

4. Taking into account the perspective of the individual requires commitment to promoting informed participation and to providing a high quality, safe service.

5. Implementation entails more than simply carrying out the screening tests and referring individuals to assessment whenever indicated. Specific protocols must be developed for identifying and subsequently inviting the target population. Protocols are also required for patient management in the diagnosis, treatment, and surveillance phase in order to ensure that all individuals have timely access to the proper diagnostic and treatment options.

6. Complete and accurate recording of all relevant data on each individual and every screening test performed, including the test results, the decision made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death, should be ensured. This monitoring process is of fundamental importance.

7. The quality assurance required for screening should also enhance the quality of the service offered to symptomatic patients.

8. Appropriate political and financial support are crucial to the successful implementation of any screening programme.

Recommendations and conclusions[1]

Organised vs. non-organised screening

2.1 In order to maximise the impact of the intervention and ensure high coverage and equity of access, only organised screening programmes should be implemented, as opposed to case-finding or opportunistic screening as only organised programmes can be properly quality assured **(III - A).**[Sect 2.2.1; 2.2.2; 2.2.3]

2.2 When organising a screening programme, several fundamental aspects should be considered: the legal framework, the availability and accuracy of epidemiological and demographic data, the availability of quality-assured services for diagnosis and treatment, promotional efforts, a working relationship with the local cancer registry, and follow-up for causes of death at individual level **(VI - A).**[Sect 2.2.3]

Implementing the screening programme

2.3 A population registry should be implemented for screening if not yet available, combining the most accurate and updated information about the target population **(VI - A).**[Sect 2.3.1]

2.4 If the screening policy allows for exclusions, the exact definition of the criteria should be given. Exclusions should be carefully and routinely monitored for appropriateness and quality **(VI - A).**[Sect 2.3.1.1]

2.5 In the absence of hereditary syndromes people with a positive family history should not be excluded from CRC screening programmes **(III - B).**[Sect 2.3.1.2]

2.6 Subjects belonging to families with hereditary syndromes, identified at the time of screening, should be referred to special surveillance programmes or family cancer clinics, if available **(III - B).**[Sect 2.3.1.2]

Participation in screening

2.7 Access to screening and any follow-up assessment for people with abnormal test results should not be limited by financial barriers. In principle, screening should be free of charge for the participant **(I - A).**[Sect 2.4.2.1]

2.8 In the context of an organised program, personal invitation letters, preferably signed by the general practitioner, should be used. A reminder letter mailed to all non-attenders increases attendance rate and is therefore recommended (see also Chap. 10, Rec. 10.7) **(I - A).**[Sect 2.4.3.1; 2.4.3.2; 10.4.1.2]

2.9 Although more effective than other modalities, phone reminders may not be cost-effective (see also Chap. 10, Rec. 10.8) **(I - B).**[Sect 2.4.3.2; 10.4.1.2]

2.10 Provision of information is necessary to enable subjects to make an informed choice, but it is not sufficient to enhance participation. Organisational measures enabling people to attend screening should be implemented **(I - A).**[Sect 2.4.3.3.1]

2.11 Primary health care providers should be involved in the process of conveying information to people invited for screening (see also Chap. 10, Rec. 10.6) **(II - A).**[Sect 2.4.3.4; 2.4.3.4.1; 10.4.1.1]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

2.12 General practitioners or family physicians (or primary health care practitioners, where preventive services are not primarily based on primary care physicians) should be involved in the implementation of organised programmes **(I - A).**^{Sect 2.4.3.4.2}

2.13 Reducing organisational barriers to physicians' advice should be a priority for interventions aimed at promoting GPs' involvement in organised screening programmes **(I - B).**^{Sect 2.4.3.4.2}

Testing protocol

2.14 For FOBT-based screening programmes, the choice of the kit provider should aim to maximise accessibility for the target population **(II - A).**^{Sect 2.5.1.1}

2.15 Mailing of FOBT kits may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics) as well as factors that might influence cost-effectiveness (such as the expected effect on the participation rate) (see also Chap. 10, Rec. 10.9) **(II - B).**^{Sect 2.5.1.1; 10.4.1.3}

2.16 Clear and simple instructions should be provided with the kit (see also Chap. 10, Rec. 10.10) **(V - A).**^{Sect 2.5.1.1; 10.4.1.3}

2.17 In order to enhance compliance, testing procedures that require no or only minor dietary restrictions are preferred **(I - A).**^{Sect 2.5.1.2}

2.18 Systematic (preferably automated) check protocols should be implemented in order to ensure correct identification of the screenee's test results and recognition of incomplete or erroneous data **(VI - A).**^{Sect 2.5.1.3}

2.19 Protocols should be in place to ensure standardised and reliable classification of the test results **(VI - A).**^{Sect 2.5.1.3}

2.20 Bowel preparation for screening sigmoidoscopy should preferably involve a single procedure. Cultural factors should be taken into account and population preference should be assessed. **(II - B).**^{Sect 2.5.2.2}

2.21 For screening sigmoidoscopy, several providers should be available that are close to the target population. Organisational options include the possibility of having the enema administered at the endoscopy unit. Clear and simple instructions should be provided with the preparation **(II - B).**^{Sect 2.5.2.2}

2.22 To date no single bowel preparation for colonoscopy has emerged as consistently superior over another in terms of efficacy and safety **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see Ch. 5, Rec. 5.22) **(VI - A).**^{Sect 2.5.2.3; 5.3.3}

2.23 For colonoscopy, several providers should be available that are close to the target population. Clear and simple instructions should be provided with the preparation **(VI - B).**^{Sect 2.5.2.2 ;2.5.2.3}

Management of people with positive test results and fail-safe mechanism

2.24 In order to ensure timely and appropriate assessment, an active follow-up of people with an abnormal screening test result should be implemented, using reminders and computerised systems for tracking and monitoring management of these patients **(II - A).**^{Sect 2.5.3}

2.25 The cost charged to the participant undergoing assessments should be as low as possible in order to promote equity of access **(II - A).**^{Sect 2.5.3}

Screening policy within the healthcare system

2.26 Gender and age-specific screening schedules deserve careful attention in the design and implementation of screening interventions **(III - C).**^{Sect 2.6.3.1}

2.27 The costs of screening organisation (including infrastructure, information technology, screening promotion, training and quality assurance), the occurrence of adverse effects and the likelihood that patients will actually complete the tests required for any given strategy represent additional important factors to be taken into account in the design and implementation of screening interventions and in the choice of the screening strategy **(III - A).**^{Sect 2.6.1-3; 2.6.3.2-5}

Implementation period (step-wise)

2.28 Ideally, any new screening programme should be implemented using individual level randomisation into screening and control groups in the phase in which resources and practical limitations prohibit the full coverage of the target population **(VI - A).**^{Sect 2.6.4}

Data collection and monitoring

2.29 In order to be able to evaluate the effectiveness of screening, the data must be linked at the individual level to several external data sources including population register, cancer or pathology registries, and registries of cause of death in the target population. Therefore, legal authorisation should be put in place when the screening programme is introduced in order to be able to carry out programme evaluation by linking the above-mentioned data for follow-up **(VI - A).**^{Sect 2.6.5.1; 2.6.5.2}

2.1   Introduction

National and organised, population-based cancer screening programmes have been in place since the early 1960s, when cervical cancer screening was first implemented in Finland. In fact, the concept of organised screening has largely been built on this experience. The effectiveness of a programme can be measured by the reduction of mortality from the specific cancer site, and this depends on the extent of organisation, i.e. how well different factors in the screening process can be linked together. These factors include the identification of the target population, the performance of the test, and diagnostics and treatment of those who need further assessment or treatment after the primary screening test (Läärä, Day & Hakama 1987; Quinn et al. 1999).

The effectiveness of screening with regard to its impact on mortality and incidence of CRC is a function of the quality of the individual components of the process, from the organisation and administration up to the assessment, treatment and follow-up of screen-detected lesions.

Fundamental to the success of a screening programme is that people in the target population are actually screened. The uptake rate is a critical determinant of the impact of screening on the reduction of CRC incidence and mortality at the population level. Equity of access to screening is clearly as important a challenge as is high compliance in new screening programmes. Understanding the reasons for non-participation is helpful in the planning phase when considering factors that should be taken into account in the design of the screening programme.

Concerns have been raised about the potential conflict between advocating high uptake rates and the intention to promote informed uptake, i.e. enabling people to make an informed choice about whether or not they want to be screened. The purpose of screening should be to benefit the whole community, while at the same time respecting the individual's autonomy that includes the right to refuse screening. Interventions aimed at increasing uptake should try to identify ways to minimise barriers to participation among those who have understanding of its likely benefits, limitations and harms.

2.2   Organised vs. non-organised screening

The specific policy of a screening programme determines the target age and gender and possibly the geographical area, the screening test and screening interval, and further diagnostics and treatment for those who need them.

The implementation of a population based screening programme is characterised by the definition of a specific population (by target age and geographical area), with eligible subjects being actively invited following an explicit and pre-defined protocol specifying the planned screening interval, as well as the testing and assessment procedures. Screening tests and the related assessments are usually free of charge for the target population in this context.

This policy may be implemented within different organisational contexts, but in all options a pre-defined organised protocol is required that takes into consideration the entire process.

2.2.1 Opportunistic screening or case-finding

Case-finding may take place outside an organised programme in which case it is referred to as opportunistic screening. This type of screening may be the result of a patient request or a recommendation made during routine medical consultation for unrelated conditions, or on the basis of a possible increased risk of developing colorectal cancer (family history or other known risk factors). Opportunistic screening is less efficient and more costly both in terms of resources and harms, and thus it is not recommended as an alternative to organised screening.

2.2.2 Comparison of coverage and effectiveness

Two cross-sectional surveys have assessed the increase in coverage (17% and 23%) resulting from the introduction of organised cervical cancer screening versus the pre-existing opportunistic approach (Ronco et al. 1997; Bos et al. 1998). Both in the United Kingdom and Norway the introduction of an organised screening programme was associated with a decrease in the incidence rate of invasive cervical cancer and an increase in the target population coverage, as compared to the period preceding the start of the programme when opportunistic screening was already widespread (Quinn et al. 1999; Nygard, Skare & Thoresen 2002). A decrease in the incidence rate of invasive cervical cancer in women who received organised screening compared to opportunistic screening was also observed in a cohort study (Lynge et al. 2006) and a case control study (Nieminen et al. 1999). A 20% decrease in incidence of invasive cervical cancer was observed in Turin, Italy, among women invited to an organised programme, compared with those not invited, after introduction of the organised programme in an area in which intensive opportunistic screening was already established (Ronco et al. 2005).

Similar findings have been reported by studies conducted in the context of breast cancer screening. Organised screening programmes can ensure better coverage of hard-to-reach populations, as suggested by a recent survey: compared to women undergoing opportunistic screening, participants in an organised programme were more likely to have never been screened, tended to ignore screening efficacy and were at risk of abandoning screening, as a result of their less-favourable attitudes towards prevention (Chamot, Charvet & Perneger 2007). A recent case–control study conducted in Italy showed that the introduction of breast cancer screening programmes was associated with a reduction in breast cancer mortality attributable to the additional impact of the organised programmes over and above the background spontaneous mammography activity. Compared to those not yet invited, women invited to the organised programmes showed a 25% (OR:0.75; 95%CI:0.62–.92) reduction of the risk of death from breast cancer (Puliti et al. 2008).

Available data from studies conducted in the context of CRC screening indicate that the introduction of organised programmes can have a similar impact, at least on target population coverage. A nationwide observational telephone survey, conducted in France (Eisinger et al. 2008), showed that greater compliance with reduced inequalities in the distribution across social groups was achieved in geographical departments where CRC screening was organised by health authorities.

2.2.3 Prerequisites for organised screening

The International Agency for Research on Cancer (IARC) has defined an organised screening programme as one that has the following features: 1) an explicit policy with specified age categories, method and interval for screening; 2) a defined target population; 3) a management team responsible

for implementation; 4) a health-care team for decisions and care; 5) a quality assurance structure; and 6) a method for identifying cancer occurrence and death in the population (IARC 2005).

When organising a new screening programme the following fundamental aspects should therefore be considered:

1. the legal framework for identification and follow-up of the population;

2. the availability and accuracy of the necessary epidemiological data upon which the decision to begin screening is based;

3. the availability and accessibility of essential demographic data to identify the target population and set up an invitation system;

4. the availability and accessibility of quality-assured services for diagnosis and treatment of colorectal cancer and its precursors;

5. promotional efforts to encourage participation in the programme;

6. a working relationship with the local Cancer Registry[2], if available, and causes of death registry, and maintenance of population and screening registers, to include adjustments to the programme and to ensure evaluation of the effects and follow-up for causes of death at individual level.

The evaluation of outcomes and interpretation of results from the entire screening programme are affected by these aspects, therefore the feasibility of an effectively managed programme should be piloted or built up gradually in the phase in which resources and practical limitations prohibit the full coverage of the target population. It is recognised that the context and logistics of screening programmes will differ by country and even by region. For example the prior existence of a population registry facilitates the issuing of personalised invitations, whereas the absence of a population register may encourage recruitment by open invitation. Many of these contextual differences will explain the differences in outcomes. In opportunistic screening programmes or case-finding, the aforementioned aspects are overlooked and evaluation of the benefits and possible harms will not be possible. The disadvantages also include many unnecessary screenings per person and low coverage of the entire target population, leading to low impact at the public health level. Compared with opportunistic screening, organised screening permits much greater attention to the quality of the screening process including follow-up of participants (Miles et al. 2004). Consequently, organised screening provides greater protection against the harms of screening, including over-screening, poor quality and complications of screening, including poor follow-up of participants with positive test results.

Summary of evidence

- Organised screening programmes achieve better coverage of the target population including hard-to-reach or disadvantaged groups **(IV - V)**.

- Organised screening is more effective, and hence likely to be more cost-effective than opportunistic screening or case-finding. The available evidence indicates that organised screening results in a larger reduction of invasive cancer incidence (cervical cancer) or mortality (breast cancer) **(III - IV)**.

- Organised screening provides greater protection against the harms of screening, including over-screening, poor quality and complications of screening, and poor follow-up of participants with positive test results **(III)**.

Recommendations

- In order to maximise the impact of the intervention and ensure high coverage and equity of access, only organised screening programmes should be implemented as opposed to case-finding or

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[2] If a cancer registry is lacking, registration of the target cancer should be initiated with the screening programme.

opportunistic screening as only organised programmes can be properly quality-assured **(III - A).**[Rec 2.1]

- When organising a screening programme several fundamental aspects should be considered: the legal framework, the availability and accuracy of epidemiological and demographic data, the availability of quality-assured services for diagnosis and treatment, promotional efforts, a working relationship with the local Cancer Registry, and follow-up for causes of death at individual level **(VI - A).**[Rec 2.2]

2.3 Implementing the screening programme

Organised CRC screening is a multi-step process including:

- Identification of the target population;

- Recruitment of eligible subjects;

- Delivery of screening test;

- Reporting of screening test results;

- Reassurance of people with normal results and information on the timing of the next test;

- Recall of people with unsatisfactory/inadequate screening test

- Follow-up of people with positive tests, i.e. diagnostic procedures and treatment needed, including a fail-safe system to make sure this actually happens; and

- Registration, monitoring and evaluation of the entire programme.

Issues related to programme implementation are discussed in Section 2.6.4.

2.3.1 Identifying and defining the target population

Catchment areas and target populations must be clearly defined. The necessary data include unique identification for each person, such as name, date of birth, relevant health insurance or social security numbers, general practitioner (GP) where appropriate, and contact address. Population registers or registries can in general provide such data, but they must be updated regularly to account for population migration, deaths and changes in personal details. In those countries in which population registries are based on administrative areas of small size, communication between registries is essential. Suitable registries might include population, electoral, social security, screening programme, and health service registries. Incomplete or inaccurate registries can result in certain groups (such as transients or ethnic minorities) not being invited for screening.

If an accurate, complete and regularly-updated register of the whole target population does not exist, an administrative database that combines information from available registries for all people to be included in screening should be implemented for the purposes of the programme. The legal basis for access to such registries must be set up and all data protection measures should be implemented according to the national and European legislation.

Recommendation

- A population registry should be implemented for screening if not yet available, combining the most accurate and updated available sources **(VI - A).**[Rec 2.3]

2.3.1.1 Inclusion and exclusion criteria

The target population for a CRC screening programme includes all people eligible to attend screening on the basis of age and geographical area of residence. However, each programme may apply additional exclusion/inclusion criteria to identify the population eligible for screening. Potential reasons for excluding a subject from screening might include conditions in which offering the screening test is not appropriate, such as terminal illness (no benefit could be attained through screening), recent (the relevant period should be specified and justified) screening test (the expected benefit achievable by repeating the test might not outweigh the risks associated with the procedure), previous diagnosis of CRC or pre-malignant lesions (these patients should already be followed-up according to specific surveillance protocols, and their inclusion in screening might result in the offer of conflicting management options).

The extent to which such individuals can be identified and excluded from the target population will vary by screening programme: for some programmes it may not be feasible or desirable to identify every category of potential exclusion prior to invitation.

The necessary information may be collected at the first personal contact with the screenee, i.e. at the time of a possible colonoscopy assessment in the case of FOBT programmes, or at the time of the screening exam for FS or colonoscopy programmes.

Exclusion might alternatively be based on the information gathered through the GPs or other primary care providers, who may be requested to check the eligibility of their patients ear-marked for invitation.

If the screening policy allows for exclusions, the exact definition of the respective criteria should be given and exclusions should be carefully and routinely monitored for appropriateness and equity.

Recommendation

If the screening policy allows for exclusions, the exact definition of the criteria should be given. Exclusions should be carefully and routinely monitored for appropriateness and equity **(VI - A).**[Rec 2.4]

2.3.1.2 Family history

People with a positive family history for CRC are sometimes considered for exclusion from screening programmes targeting average-risk people.

Implementing this option requires the adoption of procedures for identifying people with a positive family history and accurately collecting the information that is relevant to assess an individual's level of risk. It is also necessary to ensure that an alternative organised programme is in place for this group of people.

Specific surveillance protocols based on colonoscopy at shorter intervals and starting at a younger age have been shown to be effective and are recommended for members of families with hereditary syndromes. However, it is still not clear if more intensive surveillance for people at moderate risk can achieve a favourable cost-benefit ratio (Sondergaard, Bulow & Lynge 1991; Benhamiche-Bouvier et al. 2000; Nakama et al. 2000; Johns & Houlston 2001; Church 2005; Baglietto et al. 2006; Butterworth, Higgins & Pharoah 2006; Menges et al. 2006; Cottet et al. 2007) **(III)**.

If an alternative option (i.e. access to a specific surveillance protocol) is not available, people with positive family history should not be excluded from a population-based screening programme as screening offers the opportunity of access to an intervention that may ensure protection for people who would not be otherwise be covered.

Furthermore, family history, in the absence of hereditary syndromes, does not represent an indication for changing standard surveillance protocols (see Ch. 9, Sect. 9.2.3.2, Rec. 9.13). In a recent study, the characteristics of the neoplasm rather than individual's family history were found to be associated with the risk of recurrence among subjects not fulfilling the Amsterdam criteria. This suggests that these people could be considered at moderate risk of developing CRC and that surveillance intervals of more than five years may be appropriate in these cases (Dove-Edwin et al. 2005). Therefore, family history should not represent a criterion for exclusion from the screening programme, even for patients identified at the time of assessment.

Summary of evidence

Members of families with hereditary syndromes should follow specific surveillance protocols based on colonoscopy at shorter intervals and starting at a younger age **(III)**.

Recommendations

- In the absence of hereditary syndromes people with a positive family history should not be excluded from CRC screening programmes **(III - B).**[Rec 2.5]

- Subjects belonging to families with hereditary syndromes identified at the time of screening should be referred to special surveillance programmes or family cancer clinics, if available **(III - B).**[Rec 2.6]

2.4 Participation in screening

The planning and implementation of screening programmes should take into account cultural, behavioural, economic and organisational factors.

2.4.1 Barriers

Several factors influencing participation have been identified related to individual's characteristics, the setting and the organisation of the intervention and the knowledge, attitudes and practice of the provider (Vernon 1997; Jepson et al. 2000). The findings concerning the relative weight of these factors are not consistent across studies assessing determinants and barriers to participation. However, the variability of the reported findings is probably related to the different conditions under which the examined screening interventions have been implemented.

The organisation of screening within health services appears, in most countries, to be a major determinant of participation rate. Lack of insurance coverage and cost of the test have been identified as the main negative influences on participation for all screening interventions and tests. Also, lack of resources is the most likely explanation for the negative association of lower socio-economic status with completion of CRC screening tests (Sutton et al. 2000; McCaffery et al. 2002; Cokkinides et al.

2003; Slattery, Kinney & Levin 2004; Dassow 2005; Wardle, Miles & Atkin 2005). Other factors related to service organisation which were fairly consistently related to poor screening attendance are the amount of time required to perform screening, distance from the test provider and lack of physician recommendation **(III - V)**.

Knowledge and perceived benefits of screening, perceived risk of CRC and health motivation were associated with higher participation in most of the studies assessing the influence of these determinants. Worry about pain, discomfort, or embarrassment associated with the test, or fear of test results were also consistently associated with a lower attendance (James, Campbell & Hudson 2002; Montano et al. 2004; Weinberg et al. 2004; Wardle, Miles & Atkin 2005; Lawsin et al. 2007) **(V)**.

Gender and age differences in participation to CRC screening have also been reported; most studies have shown a trend to decreased participation among older people, although these findings have not been confirmed by all investigators. It has been reported that participation may be higher among women for FOBT screening and among men for endoscopy screening (James, Campbell & Hudson 2002; McCaffery et al. 2002; Menon et al. 2003; Slattery, Kinney & Levin 2004; Wardle, Weinberg et al. 2004; Dassow 2005; Miles & Atkin 2005; Segnan et al. 2005; Lawsin et al. 2007) **(V)**.

Support from a partner probably explains the positive association of marriage with screening uptake. This is more prominent in males. One reason for these findings could be that women have prior experience of screening (breast, cervix) and may therefore need less support to participate (Sutton et al. 2000; Menon et al. 2003; Wardle, Miles & Atkin 2005; Malila, Oivanen & Hakama 2008) **(V)**.

2.4.2 Interventions to promote participation

A systematic review (Stone et al. 2002), assessed the effectiveness of the following on improving screening participation: regulatory and legislative actions (outside the medical care organisation), financial incentives for providers or patients, organisational change (changes in clinical procedures or facilities and infrastructures), reminders for providers and screenees, provider feedback, education and visual materials. The most effective was the implementation of organisational changes that made delivery of these services a routine part of patient care (establishing separate clinics devoted to screening, involving nursing or clerical staff in the delivery of services, adoption of monitoring and quality improvement approaches), reducing, or eliminating costs for the individual or establishing a system of reminders.

2.4.2.1 Removing financial barriers

Experimental studies conducted in the context of breast cancer screening showed that reduced charges for screening are effective in encouraging uptake among disadvantaged groups (Jepson et al. 2000). Sending an FOBT with a postage-paid envelope for returning the sample resulted in a significantly higher uptake, compared to non-postage (Jepson et al. 2000). The return rate was highly significant for medically uninsured people in one of the studies (Miller & Wong 1993). Offering a free FOBT in addition to educational intervention was superior to the educational intervention alone in promoting completion of screening (Plaskon & Fadden 1995). Offering financial incentives to subjects invited for screening was not found to have an impact on participation (Jepson et al. 2000).

Summary of evidence

- Free-of-charge screening is associated with increased participation, including participation of disadvantaged groups **(I)**.

- The implementation of organisational changes that make delivery of screening a routine part of health care (establishing a system of reminders, establishing separate clinics devoted to screening, involving nursing or clerical staff in the delivery of services, adoption of monitoring and quality improvement approaches) represent the most effective interventions to enhance participation rate **(I)**.

Recommendation

- Access to the screening tests and to the follow-up assessment for individuals with abnormal test results should not be limited by financial barriers. In principle access should be free of charge for the participant **(I - A).**[Rec 2.7]

2.4.3 Invitation

2.4.3.1 Invitation letter

Strong evidence indicates that receiving a letter signed by the GP increases screening uptake, compared to receiving letters signed by other figures of authority (Jepson et al. 2000; Cole et al. 2002; Federici et al. 2005).

A personal invitation letter from the GP is also associated with increased participation when the FOBT kit is delivered by mail (Cole et al. 2002).

It should be considered however that individuals can be encouraged to participate through support provided by other trusted health care professionals. In the Nordic countries, for example, invitation letters are not signed, but refer to the local authorities, and the observed participation rates are very high (70%) (Malila, Oivanen & Hakama 2008).

A positive impact on participation due to the offer of a pre-fixed appointment has been reported by several studies of breast and cervical cancer screening (IARC handbook vol 10, (IARC 2005) and has also been confirmed among people invited for FS screening. Inviting people to obtain the FOBT kit within a pre-defined time interval, or offering a pre-defined appointment for kit delivery has been adopted in some programmes, but comparative data on the impact of these strategies are lacking.

Data from a recent trial (Cole et al. 2007) indicate that an advance notification letter significantly increases participation in FOBT screening (from 39.5% to 48.3%). The effect was explained by a population shift in readiness to undertake screening.

2.4.3.2 Reminders

In the English NHS Screening Programme over 50% of participants only respond after receiving a reminder about 28 days after receiving their initial postal invitation. A well-conducted review (Jacobson & Szilagyi 2005) that assessed the effectiveness of different kinds of reminders (reminder and recall systems delivered by letter; postcard; telephone; auto-dialler; or in person, e.g. a provider gives face-to-face reminder) concluded that all kinds of reminders are effective, with telephone reminders being the most effective, but also the most costly.

Summary of evidence

- A personalised letter signed by the general practitioner or by another trusted primary health care provider is more effective than an impersonal letter sent by a central screening centre **(I)**.

- An advance notification letter may increase participation **(II)**.

- Any kind of reminder is effective in increasing participation, with telephone reminders being the most effective although the most costly option **(I)**.

Recommendations

- In the context of an organised programme, personal invitation letters, preferably signed by the GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation **(I - A).**[Rec 2.8]

- Although more effective than other modalities, phone reminders may not be cost-effective **(I - B).**[Rec 2.9]

2.4.3.3 Delivering information about screening

Although the organisation of screening within health services emerges as the most important determinant of uptake, factors related to culture, values and beliefs may still play a role. Also, provision of information is clearly necessary to enable subjects to make an informed choice.

Data from the National Health Interview Survey (NHIS) consistently indicate that lack of awareness of CRC represents one of the main determinants of the underutilisation of screening.

Data from people recruited in the UK sigmoidoscopy trial (Wardle et al. 2004) who were requested to express their intention to attend screening suggest that part of the explanation of the socio-economic status (SES) gradient may be the difference in beliefs and expectations. Lower social groups evaluated the offer of a screening test, which had been publicised identically and was provided free of charge , at a convenient location and time, to all social groups, as being more frightening and less beneficial, than higher social groups. In England, with overall population participation at 60% despite free testing, the uptake rate of the FOBT programme is lower in deprived areas and among ethnic minorities (von Wagner et al 2009). Rural areas were shown to have a lower participation rate than urban areas (Launoy et al. 1993; Giorgi Rossi P. et al. 2005).

Therefore, the way the population is informed about the potential benefits and harms of screening is of particular importance. Strategies aimed at improving population knowledge and awareness of CRC and screening should target health professionals as well as individuals (see also Chapter 10).

Most programmes provide written information in the form of leaflets to people invited for screening. (see also Chapter 10).

Mass-media campaigns are also implemented, to support enrolment in organised programmes (see also Chapter 10).

Interventions aimed at promoting health professionals practice and communication with people invited for screening is discussed in Section 2.4.3.4.1 when considering the role of GPs/family physicians (see also Chapter 10).

2.4.3.3.1 Information conveyed with the invitation (see also Chapter 10)

A systematic review of methods aimed at enhancing screening rates concluded that educational interventions are less effective than organisational changes and should not be the first choice (Stone et al. 2002). Findings from more recent studies (Harris et al. 2000; Lipkus, Green & Marcus 2003; Robb et al. 2006; Costanza et al. 2007) support such a conclusion. When individuals interested in screening were requested to actively seek further information and a referral to screening from their providers, an information brochure was observed to have no impact, but the number of screening requests in-

creased significantly when the GP delivered an FOBT request form together with the information pamphlet.

The content and format of the information material sent with the invitation may influence a subject's decision to undertake screening (see also Chapter 10). An individually tailored interactive multimedia programme at the physician's office seemed more efficacious in increasing readiness to undergo screening, as compared to the same intervention not individually tailored (Jerant et al. 2007). Interventions that use visual instruments to enhance appeal and clarity are more effective: adding illustrations about the polyp-cancer process and the removal of the polyps during FS to written material was associated with a significant increase in knowledge and understanding (Brotherstone et al. 2006). Culturally and linguistically appropriate approaches promoting FOBT can enhance screening practice in groups of low-income and less acculturated minority patients (Tu et al. 2006).

Summary of evidence

- The impact of information conveyed with the invitation is greater if the invitation is signed by an individual's physician. Involvement of GPs also shows a positive influence on the impact of more tailored and structured information methods **(II)**.

Recommendations

- Provision of information is necessary to enable subjects to make an informed choice, but it is not sufficient to enhance participation. Organisational measures should be implemented in order to enhance participation in screening **(I - A).**[Rec 2.10]

2.4.3.4 The role of primary care providers

Primary health care providers can be effective media for improving awareness of the risk of cancer and of the benefits of screening, for increasing confidence in the screening test method and for countering the reluctance to collect faecal samples. In many European countries this provider is the general practitioner (GP), but other trusted health professionals, such as community nurses for example, may play a similar role.

Primary health care providers should be trained to deliver evidence-based information on screening and there should be a consensus on the programme protocol before starting the programme.

2.4.3.4.1 Role of GPs/family physicians

The involvement of GPs in screening can be very effective in improving compliance, according to the findings of several studies from different countries (Launoy et al. 1993; Tazi et al. 1997; Grazzini et al. 2000; Brawarsky et al. 2004; Federici et al. 2006; Sewitch et al. 2007; Seifert et al. 2008), but the effect is dependent upon the GP's own willingness to get involved. The findings of studies conducted in the context of opportunistic screening showed that the probability of not receiving a GP recommendation for CRC screening was highest among those with a low socioeconomic status (SES) (Brawarsky et al. 2004; Wee, McCarthy & Phillips 2005; Klabunde, Schenck & Davis 2006; Schenck, Klabunde & Davis 2006). These findings suggest that inadequate provider counselling represents an important determinant of the SES gradient in screening uptake. Compliance was shown to be closely linked to practitioner motivation also in the context of organised programmes (Launoy et al. 1993; Federici et al. 2006).

Knowledge of GP attitudes and preferences is therefore crucial in enhancing participation. A study based on semi-structured questionnaires addressed to 32 GPs in England (Woodrow et al. 2006) indicated that for GPs to effectively promote screening they must have adequate information prior to the start of a screening programme. The evidence should be based specifically on the effectiveness of the

screening programme, and information on the proportion of false negatives and the proportion of false positives.

Summary of Evidence

- The implementation of organisational measures aimed at facilitating participation in screening is required in order to achieve the expected impact of educational interventions **(II)**.

Recommendation

- Primary health care providers should be involved in the process of conveying information to people invited for screening **(II - A).**[Rec 2.11]

2.4.3.4.2 Interventions aimed to promote provider involvement (See also Chapter 10)

Provider education has been identified as a potentially effective intervention to promote CRC screening utilisation, even if the implementation of organisational measures may be necessary to achieve an impact of educational efforts (Stone et al. 2002). This conclusion is supported by the results of recent experimental studies: educational seminars offered to physicians did not show an effect on rates of CRC screening (Walsh et al. 2005), while a reminder note to the physician to direct his patients to perform an FOBT was more effective than a mail reminder and as effective as a phone reminder for the patients.

Even if GPs are not delivering kits, or not collecting or reading the test cards, they should be aware of how the programme, and in particular the invitation scheme, is structured. They can advise non-compliers about screening, which is important for older people, or for those with lower socio-economic status, and they can offer counselling for patients with positive tests. To facilitate this task, GPs should receive the results of screening and assessment tests performed by their patients.

Summary of evidence

- Primary health care providers appear to be effective media for improving awareness of the risk of cancer and the benefits of screening, and increasing confidence in and countering the reluctance to take the screening test **(I)**.

- Educational interventions are less effective than organisational changes in improving the impact of physicians' counselling on their patients' screening rates **(I)**.

Recommendations

- GPs or family physicians (or primary health care practitioners where preventive services are not primarily based on primary care physicians) should be involved in the implementation of organised screening programmes **(I - A).**[Rec 2.12]

- Reducing organisational barriers to physician's advice should be a priority for interventions aimed at promoting GP involvement in organised screening programmes **(I - B).**[Rec 2.13]

2.5 Testing protocol

2.5.1 FOBT

2.5.1.1 Delivery of kits and collection of stool samples (see also Chapter 4)

The test kit may be delivered by mail, at GPs' offices or outpatient clinics, by pharmacists, or in other community facilities, and in some cases with the support of volunteers. There is no evidence that any of these strategies may have an impact on the proportion of inadequate samples, provided that clear and simple instruction sheets are included with the kit (Courtier et al. 2002; UK Colorectal Cancer Screening Pilot Group 2004; Zorzi et al. 2007).

The choice of the provider should aim to maximise accessibility, taking into account local conditions, settings and cultural factors.

Mailing of the FOBT kit with instructions, together with the invitation letter and the information leaflet, is effective in increasing participation rates (Church et al. 2004; Segnan et al. 2005). These results are consistent with previous reports indicating that the GP's letter and mailing of FOBT kits represent the most important factors for improving compliance (King et al. 1992). Mailing of the FOBT kit might not always represent a cost-effective strategy, if the baseline participation rate and the expected increase in participation are low. Compared to mailing a second FOBT kit to all non-responders, mailing a recall letter with a test order coupon resulted in a substantial decrease in the programme costs, but also in a significant decrease in participation (Tifratene et al. 2007). The authors of the trial suggested, however, that the spared costs might be allocated more efficiently to communication interventions that might have a higher impact on compliance.

Several test providers close to the target population should be available when the subject is required to reach health or community facilities to get the kit. A recent study (Federici et al. 2006) showed that the time required to reach the test provider was the strongest determinant of compliance: OR (<15 minutes versus 15–30 or >30 minutes):0.8 (0.5–1.3) and 0.3 (0.2–0.7) respectively.

Volunteers or non-health professionals may also be involved in the distribution and collection of kits. Delivery of kits may represent in this case an additional opportunity for counselling, for conveying information about the programme and for providing instructions for test utilisation. Subjects contacted at home by a trained non-health professional who delivered the kit and collected the sample from the participant's home showed a substantially higher completion rate of iFOBT, as compared to the group who received the kit by mail with an invitation from their primary care physician, (Courtier et al. 2002).

Community volunteers, who have received some general training by the programme staff, have been involved in the kit distribution in the context of ongoing organised programmes and their involvement has been consistently associated with high participation rates (Zorzi et al. 2007). As no randomised comparison is available, it is difficult to dissociate their specific effect from other characteristics of the communities or target populations involved. Sustainability over time represents an important issue to be taken into account when planning to use volunteer support.

The modalities adopted for stool collection, storage and shipping of the sample to the laboratory are mainly dependent on the characteristics of the test adopted, i.e. its stability at environment temperature. Based on these considerations mailing of the samples may be an option that can be implemented more easily for guaiac than for immunochemical tests, which need to be processed faster. Accessibility of the collection facilities remains an important goal, but the logistics of the sample han-

dling may promote reducing the number of collection facilities in order to ensure an appropriate storage or timely shipping to the laboratories.

See also Chapter 4 for tests characteristics and storage requirements.

Summary of evidence

- There is no evidence that the proportion of inadequate samples may be affected by the provider used to deliver the kit, if clear and simple instruction sheets are provided with the kit **(II - V)**.

- The time required to reach the test provider represents a strong determinant of compliance **(II)**.

- Sending the FOBT kit together with the invitation letter may be more effective than sending a letter alone, but this strategy may not be cost-effective **(II)**.

Recommendations

- The choice of the kit provider should aim to maximise accessibility of the target population **(II - A).**[Rec 2.14]

- Mailing of FOBT kit may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics), as well as factors that might influence cost-effectiveness (such as the expected impact on participation rate) **(II - B).**[Rec 2.15]

- Clear and simple instruction sheets should be provided with the kit **(V - A).**[Rec 2.16]

2.5.1.2 Performing the test: dietary restrictions and number of samples

In order to reduce the probability of a false positive result, dietary restrictions are usually recommended when guaiac-based tests are used. Retesting of subjects with a positive test (possibly with dietary restrictions being recommended) represents an alternative option adopted in some programmes to deal with this problem. A review of 5 trials (10 359 participants overall) comparing Guaiac FOBT with and without dietary restriction found a significant difference in compliance in favour of testing without dietary restrictions only in the trial where restrictions were particularly extensive. Authors concluded that advice to restrict the diet and avoid NSAIDs and vitamin C does not substantially reduce completion rate except perhaps when the dietary restrictions are particularly extensive (Pignone et al. 2001). More recent randomised trials (Cole et al. 2003; Federici et al. 2005; van Rossum et al. 2008) have demonstrated that better compliance can be achieved using iFOBT compared to a guaiac-based test. These results are not explained by the nature of the test but by lack of dietary and drug restrictions and easier and more pleasant sampling methods. Indeed, dietary restriction was associated with a significant decrease in participation also among people offered iFOBT test, compared to controls receiving the same test who where not advised to control their diet (Cole & Young 2001).

Summary of evidence

- Compliance is affected by dietary restriction and number of stool samples to be collected. Compliance is found to be consistently higher when the test adopted does not require modification of a subject's diet and sampling is limited to one bowel movement **(I)**.

Recommendation

- In order to enhance compliance, testing procedures that require no or only minor dietary restrictions are to be preferred **(I - A).**[Rec 2.17]

2.5.1.3 Examination of the samples, test interpretation and reporting

Detailed protocols on handling the stool samples must be available and followed. Identification and tracing of the sample through the entire process should be ensured by adopting appropriate labelling

allowing the sample and patient's ID code to be linked. Automated check protocols should be implemented in order to avoid mismatching of the results. All data, including test results, should have a regular backup system.

Guidelines for the equipment, organisation, quality assurance (within and between laboratories) to be adopted for different FOB tests, as well as the professional requirements for the staff, are described in Chapters 4 and 6.

An operational definition for an inadequate screening test should be made explicit in the programme protocol, taking into account the characteristics of the test (i.e. the stability and the storage requirements of the tests) as well as the testing procedure adopted (i.e. the number of samples or of cards required) (see Sect. 2.5.4.2.1 and 2.5.4.2.2).

Protocols should be in place to define the appropriate test and the algorithm used to classify a test result (as negative or positive). For quantitative or semi-quantitative iFOBTs, an explicit definition of cut-off levels for haemoglobin concentration should be defined. Protocols or rules for combining results when using multiple samples, the number of samples that are needed to evaluate the test result, etc. must be in place. When using a quantitative test, provision should be made to record the information concerning the actual amount of haemoglobin, both for tests classified as negative and for those classified as positive.

Some people may present with clinical conditions such as inflammatory bowel disease (Crohn's disease or haemorrhagic recto-colitis), which may explain a positive FOBT result. In such cases, if no cancers were detected, then the screening result should be classified as negative for the purposes of the screening programme. These patients should then be referred for treatment in the appropriate clinical setting.

See Chapter 10 for a discussion of information about negative test results.

Recommendations

- Systematic (preferably automated) check protocols should be implemented in order to ensure correct identification of the screenee's test results and recognition of incomplete or erroneous data **(VI - A).**[Rec 2.18]

- Protocols should be in place to ensure standardised and reliable classification of the test results **(VI - A).**[Rec 2.19]

2.5.2 Endoscopy

2.5.2.1 Obtaining bowel preparation for endoscopy screening

The bowel preparation may be obtained from the office of the primary health care provider (e.g. GP), from endoscopy units or other screening facilities, or from pharmacists. There is no evidence concerning the impact of any of these strategies on participation rate, or on the proportion of inadequate exams. The aim should be to maximise accessibility taking into account local conditions, setting and culture. Several providers close to the target population should be available. The bowel preparation should be provided with clear and simple instruction sheets (see also Chapter 5).

2.5.2.2 Bowel preparation for sigmoidoscopy (see also Chapter 5)

The acceptability of different types of preparations is influenced by cultural factors, which should be considered together with the evidence concerning the effect of the preparation, when choosing among different options. No difference in the proportion of inadequate exams was observed when comparing a single enema regimen to a preparation using two enemas or to oral preparation (Senore et al. 1996; Atkin et al. 2000).

Summary of evidence

- A bowel preparation regimen using a single enema self-administered at home two hours before the endoscopy has been reported as the most acceptable option **(II)**.

- Using two enemas may not decrease participation, while a preparation using both oral preparation and enema has a negative effect on compliance **(II)**.

Recommendations

- Bowel preparation for screening sigmoidoscopy should involve a single procedure, either enema or oral preparation. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and population preference should be assessed **(II - B).**[Rec 2.20]

- Several providers of bowel preparation close to the target population should be available when the subject is required to reach health or community facilities to get the preparation. Organisational options include the possibility of having the enema administered at the endoscopy unit. Clear and simple instruction sheets should be provided with the preparation **(II - B).**[Rec 2.21]

2.5.2.3 Bowel preparation for colonoscopy (see also Chapter 5)

Data on the impact of different preparation regimens in the context of population screening with colonoscopy are lacking. A recent systematic review (Belsey, Epstein & Heresbach 2007) concluded that no single bowel preparation emerged as consistently superior, but sodium phosphate was better tolerated. The authors identified a need for rigorous study design to enable unequivocal conclusions to be drawn on the safety and efficacy of bowel preparations (see Ch. 5, Sect. 5.3.3).

Timing of administration of the recommended dose appears important, as it has been established that split dosing (the administration of at least a portion of the laxative on the morning of the examination) is superior to dosing all the preparation the day before the test, both for sodium-phosphate and poly-ethylene glycol (Aoun et al. 2005; Parra-Blanco et al. 2006; Rostom et al. 2006; Cohen 2010) **(II)**

Summary of evidence

- To date no single bowel preparation for colonoscopy has emerged as consistently superior over another in terms of efficacy and safety **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II).**

Recommendations

- Preparation regimes used for colonoscopy seem equivalent in terms of efficacy and safety, although sodium phosphate may be better tolerated **(I)** and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see also Ch. 5, Rec. 5.22, Sect. 5.3.3) **(VI - A).**[Rec 2.22]

- Several providers close to the target population should be available when the subject is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation **(VI - B).**[Rec 2.23]

2.5.2.4 Test interpretation and reporting

2.5.2.4.1 Inadequate test

As mentioned above (Sect. 2.5.1.3), an operational definition for an inadequate screening test should be made explicit in the programme protocol, taking into account the characteristics of the test as well as the testing procedure adopted .

2.5.2.4.2 Defining a negative test and episode result

An explicit protocol defining the conditions for classifying a test as negative should be adopted, specifying the criteria for referral to colonoscopy assessment (in FS-based programmes) or surveillance (TC-based programmes).

Also, an operational definition for a negative screening episode should be made explicit in the programme protocol. A screening episode should be classified as negative when, based on the results of the primary test or of the recommended assessments (if any), the subject is referred again to the standard screening protocol. The rationale for having such pragmatic definition is to avoid the risk of labelling people detected with lesions that do not have clinical and prognostic significance (see also Chapter 10). This approach allows concomitant measurement of the detection rates for various types of lesions that are included among the performance indicators listed in Chapter 3.

See Chapter 10 for details on how to communicate information about negative and positive test results.

2.5.3 Management of people with positive test results and fail-safe mechanisms

The potential reduction of mortality through cancer screening can only be achieved if subjects with abnormal findings receive timely and appropriate follow-up for detected abnormalities.

The findings of a recent US survey indicated that less than 15% of health plans monitor receipt of appropriate follow-up care by patents with abnormal results. This lack of organised tracking systems probably explains the low proportion of people with abnormal screening findings who receive adequate follow-up (Yabroff et al. 2003). In particular, among patients receiving FOBT screening in the Veterans health administration, 41% of those with a positive test failed to receive appropriate assessment (Etzioni et al. 2006). The negative implications of follow-up failures are substantial, including at the population level. A previous analysis of the screening history of invasive cervical cancers identified by a population-based cancer registry showed that about 20–25% of women with invasive cancer had been recommended for an early repeat smear, but had not received adequate follow-up (Bucchi & Serafini 1992).

Effective interventions targeting the screen-positive individuals include (Bastani et al. 2004): reducing financial and other barriers for further investigations or eliminating the costs for the patients, mail or telephone reminders, and providing written information material or telephone counselling addressing

fears related to abnormal findings. All these interventions were found to be successful in increasing the proportion of people receiving timely follow-up. Few interventions have been assessed at the practice/provider level. The offer of same-day follow-up on-site colposcopy for abnormal Pap-smears (Holschneider et al. 1999) or an on-site colonoscopy following a positive sigmoidoscopy (Stern et al. 2000), has led to improved patient compliance. In a predominantly minority and indigent population targeted for cervical cancer screening, subjects managed through a specialised clinic, including nurse case manager, tracking system, reminder calls, rescheduling of missed appointments and clinical staffing with on-site colposcopy, achieved a significantly increased follow-up compared to a randomly assigned control group (Engelstad et al. 2001). The implementation of infrastructure (computerised systems for tracking and monitoring of screening abnormalities) and organisational changes (multidisciplinary team work) are required to ensure sustainability over time of effective interventions.

Treatment and after-care service following evidence-based guidelines should be offered to all patients detected with cancer or pre-invasive lesions at the time of assessment of abnormal screening findings.

Summary of evidence

- Reducing the financial barriers for further investigations, utilisation of mail or telephone reminders, written information material or telephone counselling addressing fears related to abnormal findings, implementation of computerised systems for tracking and monitoring of screening abnormalities and organisational changes (multidisciplinary team work) were found to be successful in increasing timely follow-up **(II)**.

Recommendations

- In order to ensure timely and appropriate assessment, active follow-up of people with screening abnormalities should be implemented, using reminders and computerised systems for tracking and monitoring management of these patients **(II - A).**[Rec 2.24]

- The cost to the participant undergoing assessments should be as low as possible in order to promote equity of access **(II - A).**[Rec 2.25]

2.5.4 Follow-up of population and interval cancers (see also Chapter 3)

The ascertainment of interval cancers represents a key component of the evaluation of a screening programme. The documentation and evaluation process requires forward planning and linkage between screening registries and cancer registries, including data on causes of death, with no losses to follow-up. Data collection and reporting should cover all cancers appearing in the target population.

Methods of ascertainment and follow-up may differ across countries and screening programmes depending on the availability and accessibility of data and of existing data sources: cancer/pathology registries, clinical or pathology records or death records/registries. See Chapter 3 for a description of the indicators and the data requirements.

2.6 Screening policy within the healthcare system

There should be a national and governmental context for planning of CRC screening. The programme needs political support with sustainable funding to succeed. If appropriate structures in the healthcare system are lacking, screening should not be implemented until they are developed, for example using the implementation phase to build up the needed structures.

It is essential that the programme is integrated into the healthcare system and is accepted by both the population and health professionals involved in the diagnostic process for CRC. Organisation of the screening programme should integrate the structures of the entire health care system appropriately and it should comply with national guidelines and protocols. Within the organisational framework of the programme, the target population should be defined as well as the frequency of screening. Provisions should be made for the financing of the programme, including evaluation costs.

The professional and organisational managers of a screening programme must have sufficient authority and autonomy, including an identified budget and sufficient control over the use of resources to effectively control the quality, effectiveness and cost-effectiveness of the programme and the screening service. The institutional structure must facilitate effective management of quality and performance.

Process and outcome indicators should be constantly evaluated to serve the needs of the individual and the health service.

Adequate protection of all data should be ensured, following requirements set by European directives concerning data protection and national privacy legislation.

2.6.1 Local conditions at the start of a programme

Before implementation of a screening programme, an inventory of baseline conditions including information on opportunistic screening rates, background CRC incidence rates and availability of endoscopic resources should be made.

In order to run a successful programme, adequate resources, in terms of both staff and facilities must be available, and an adequate infrastructure must be in place.

Colonoscopy is the final common denominator of all the CRC screening strategies. Therefore, as the implementation of any form of population screening for CRC will place greater demands on colonoscopy resources, the feasibility of CRC screening also depends on the availability of colonoscopy services. There may also be limitations to access for subjects in rural or remote areas and in the public health sector. Clearly, CRC screening is only feasible if access can be guaranteed to individuals who participate in screening.

In many European countries, CRC early detection activity exists in some form, e.g. testing personally initiated by patients, or as a component of private health care. According to the findings of a recent survey conducted in 10 European countries and in Canada, about 10% of colonoscopies are performed for screening (Burnand et al. 2006). However a wide variation was found in the occurrence and in the appropriateness of the exams. The inappropriateness rates ranged between 0% and 50%. Similarly the proportion of colonoscopies performed following clinical indications which were judged to

be inappropriate was about 25%, suggesting overuse of the exam. Even if screening exams should be delivered within dedicated sessions (see also Chapter 5), promoting a more appropriate use of colonoscopy might therefore increase quality of care and favour an efficient use of available resources. As suggested by simulations conducted in the US (Seeff et al. 2004) a more efficient use of colonoscopy resources may result in an increase in the capacity to meet the demand of screening-induced colonoscopies.

It is unlikely, however, that simply providing funds to increase existing activity will enable the programme or screening policy to be successful. In parallel with introducing the general principles of organised screening, governments should consider the introduction of administrative measures (i.e. not paying for unnecessary exams) and implementing educational interventions aimed at enhancing appropriateness of colonoscopy referrals. In some countries, re-allocation of resources already used for opportunistic screening activities will be sufficient to cover the entire target population within a defined screening interval.

2.6.2   Defining the relevant healthcare professional and facilities

Depending on each country's health system and culture, different health professionals can be involved in kit delivery and stool sampling collection or in delivering bowel preparation for endoscopy screening (i.e. GPs, nurses, paramedics, pharmacists, volunteers from no-profit organisations, etc.), as well as in performing sigmoidoscopy when offered as a screening test (i.e. GPs, nurses gastroenterologists,). Each country should follow quality assurance standards for the facilities and establish minimum training requirements for each type of professional, fulfilling the present guidelines (see Chapter 6).

2.6.2.1 Diagnostic and treatment centres

Screening will be neither effective nor efficient if patients with a positive FOBT or FS are not followed up with a proper evaluation of the entire colon and appropriate management, if needed. Trained endoscopists are essential, and each programme should establish and monitor validated training for colonoscopy, following the guidelines in Chapter 6. To help in the planning of location of endoscopic services for screening, five levels of competency are proposed in Chapter 5 (see 5.3.1). The definitions of the proposed levels take into account the facilities and the level of competency which are necessary to remove screen-detected lesions, and consequently how often the patients should be referred elsewhere in order to have the detected lesions safely and expertly removed. If all resources are not available in a given area, large centres, particularly for diagnosis and treatment, can serve more than one area, provided that adequate communication is established.

2.6.2.2 Public health specialists

Considering the different healthcare environments, public health specialists with adequate epidemiological knowledge or equivalent expertise are recommended. These professionals are needed from the onset, to ensure that the programme includes a population-based information system that monitors each step of the screening process. They will then be responsible for gathering data and for ongoing monitoring in order to identify problems that need intervention. These public health specialists can be based at a national or regional level, whereas the other health professionals who are providing screening services are needed in each area. Public health specialists should have training in and an understanding of basic epidemiology, statistics and communication. A European training programme on monitoring and evaluation of screening programmes would be desirable (see also Chapter 6).

2.6.3 What factors should be considered when deciding which primary test to use?

According to the findings of a survey of the International ColoRectal Cancer Screening Network (ICRCSN) describing CRC screening protocols adopted in various countries, a number of diverse screening initiatives have been implemented with a wide variation in various aspects of programme implementation including the tests used for primary screening. Currently FOBT is the only primary test recommended by the EU for CRC screening (Council of the European Union 2003, Appendix 2, see Ch. 1, Sect. 1.1.4) (Benson et al. 2008).

Today there is a range of options for CRC screening in the average-risk population. The tests commonly adopted in screening interventions include tests for occult blood (either guaiac or immuno-chemical), sigmoidoscopy (FS) and total colonoscopy (TC). Whether one method is superior to the other is not clear from several analyses (Pignone et al. 2002; Zauber et al. 2008). Although clear experimental evidence is available only for FOBT, FS and TC are commonly considered as reasonable alternatives (see Chapter 1). It has been suggested that a country's screening initiative should be adapted to suit population size, healthcare system and methods of funding, and should be individualised to practice settings and if possible to people (Benson et al. 2008; Whitlock et al. 2008). Thus, when deciding which primary test to use, several factors should be considered. Some of them are connected with country-specific conditions.

2.6.3.1 Gender and age differences (see also Chapter 1)

CRC incidence and mortality are consistently lower among women than among men, and they show an increasing trend with age, although age-specific CRC incidence and mortality vary strongly within Europe. Comparative analyses of age- and gender specific CRC incidence and mortality in 38 European countries indicate that the differences across countries translate to wide age ranges at which comparable levels of risk are reached. The risk advancement attributable to these geographical differences in age-specific incidence and mortality rates across Europe has been estimated to be up to 10 years or more, while the lower incidence and mortality among women quite consistently translates to an age difference of approximately 4–8 years at which comparable levels of risk are reached (Regula et al. 2006; Brenner et al. 2007b; Brenner, Hoffmeister & Haug 2008). CRC incidence and mortality represent important parameters affecting potential benefits of screening, which must be weighed against costs and potential adverse side effects when choosing the age of screening initiation.

Cost-effectiveness modelling of different strategies was generally consistent in evaluating as efficient to begin screening between 50 and 60 (Eddy 1990; Ness et al. 2000); decreasing the stop age from 85 to 75 yielded a small reduction in life-years gained with a large reduction in the number of tests. Another important factor when assessing the age at which to stop screening is the remaining life expectancy.

2.6.3.2 Participation

Acceptability of the proposed strategy and test represents a critical determinant of the impact of an organised programme. It influences the cost-effectiveness of the most commonly recommended tests due to different levels of participation (Zauber et al. 2008). The effectiveness of an intervention is therefore influenced by the compliance level that can be achieved, and ultimately the best option for a patient is the one he or she will attend. It has been suggested that the relevant information when comparing different strategies should be the estimate of the level of relative adherence to different tests which provide comparable levels of life-years gained per number of colonoscopies. More accept-

able tests would pick up a higher proportion of prevalent lesions, even if their sensitivity were low, because more people would attend screening (Segnan et al. 2007).

Differences in exclusion criteria, if any, should be taken into account.

Thus the availability of different screening methods that would allow individuals in the target population to choose their preferred strategy based on their preferences and values does not seem to be an effective option. The offer of a choice between two tests was not associated with increased coverage in a recent trial (Segnan et al. 2005). Offering an alternative test to people refusing the main screening strategy of a screening programme might represent a feasible option (Zorzi et al. 2007). However, the sustainability and the organisational impact of such strategy should be assessed at the local level.

2.6.3.3 Screening interval and neoplasia detection rates according to the site distribution (see also Chapter 1)

Evidence from randomised trials indicates that annual guaiac FOBT is associated with a higher mortality reduction compared to biennial screening. Observational studies (Saito et al. 1995; Zappa et al. 2001) support the indication of biennial screening with iFOBT (see also Chapter 4). The recommended interval for colonoscopy screening is usually 10 years, although evidence from observational studies would indicate that the protective effect may be longer. A five-year interval is usually recommended for FS screening, although available evidence does not support such a recommendation: observational studies have indeed suggested that the protective effect of the exam for CRC arising in the distal colon may last for more than 10 years and it would justify the adoption of a protocol offering the test once in a lifetime (Selby et al. 1992; Newcomb et al. 2003).

The expected impact of endoscopic tests is also related to the site distribution of the neoplastic lesions in the colon and on their natural history (see also Chapter 1).

According to the results of a population-based case–control study, about 75–80% of colorectal cancer cases could be prevented by colonoscopy, with stronger effect for distal than for proximal CRCs (Brenner et al. 2007a). Recent cohort studies of people examined with colonoscopy confirm a protective effect of colonoscopy but suggest that the protective effect for proximal lesions might be overestimated (Lakoff et al. 2008; Baxter et al. 2009).

2.6.3.4 Cost-effectiveness (see also Chapter 1)

Available evidence from cost-effectiveness analysis suggests that all commonly considered CRC screening strategies (FOBT, FlexiSig, TC total colonoscopy) are nearly equivalent for prevention of colorectal cancer mortality (assuming 100% adherence) (Zauber et al. 2008) and they therefore represent reasonable alternatives. Compared with no screening, nearly all analyses found that any of the common screening strategies for adults 50 years of age or older will reduce mortality from colorectal cancer. The cost per life-year saved for colorectal cancer screening (US$ 10 000 to US$ 25 000 for most strategies compared with no screening) compares favourably with other commonly endorsed preventive health care interventions, such as screening mammography for women older than 50 years of age or treatment of moderate hypertension.

The costs of a screening programme are strongly affected by the organisation of screening, including the costs of infrastructure, information technology, screening promotion, training and quality assurance, and by the characteristics of the health system. These same factors represent the main determinants of the cost of the screening test, which influences the estimates of the relative costs of different strategies. The timing of the costs and benefits should be considered as well: for example, endoscopy costs are met at the beginning, while those of FOBT spread over 10 years.

Also, the advantage in terms of risk reduction must be weighed not only against the programme costs, but also against the inconvenience for the patient and the adverse effects (some of them causing death, potentially, thus mortality evaluation is also key in cost-effectiveness) associated with each strategy. These factors will influence the likelihood that patients will actually complete the tests required for any given strategy and therefore these factors also have a strong impact on the costs of the tests.

2.6.3.5 Resources and sustainability of the programme

A recent resources-use analysis of the strategies considered for the UK bowel cancer screening programmes found considerable differences between screening strategies in terms of endoscopy staffing and capital requirements. Limited availability of endoscopy services would favour the adoption of strategies using highly specific tests targeting older age groups, while a sigmoidoscopy-based strategy would be preferred if the financial resources are constrained. Also, the high number of cases detected when adopting a strategy using biennial FOBT for people aged 50 to 69 would have a significant impact on surgical services. Resource constraints, mainly related to availability of highly qualified personnel (Vijan et al. 2004) represent a strong barrier to the adoption of colonoscopy as a primary screening tool.

Summary of evidence

- The balance in favour of screening is likely to be reached at rather different ages in the various European countries, and several years later among women than among men **(III)**.

- Offering people the option to choose a preferred strategy based on individual preferences and values does not result in increased coverage **(II)**. Offering an alternative test to people refusing the main screening strategy adopted by a screening programme might represent a feasible and effective option **(V)**.

- The relative effectiveness in terms of incidence and mortality reduction of TC compared to FS might be overestimated **(IV)**.

- The costs of a screening programme are strongly affected by the organisation of screening, by the characteristics of the health system. Different strategies involve different timing of the expected costs and of the achievable benefits **(III)**.

- The impact of each specific strategy is strongly affected by its acceptability in the target population **(III)**.

Recommendations

- Gender- and age-specific screening schedules deserve careful attention in the design and implementation of screening interventions **(III - C).**[Rec 2.26]

- The costs of screening organisation (including infrastructure, information technology, screening promotion, training and quality assurance), the incidence of adverse effects and the likelihood that patients will actually complete the tests required for any given strategy represent additional important factors to be taken into account in the design and implementation of screening interventions and in the choice of the screening strategy **(III - A).**[Rec 2.27]

2.6.4 Implementation period (step-wise)

From an epidemiological perspective implementation entails more than simply carrying out the screening process and onward referral for assessment whenever required. The particular epidemiological concerns at the early, implementation phase focus on the complete and accurate recording of all indi-

vidual data pertaining to every participant, the screening test, its result, the decisions made as a consequence and their eventual outcome in terms of diagnosis and treatment and monitoring the causes of death.

Pilot demonstration projects have been carried out in some European countries to assess the feasibility of national programmes and their impact on routine services and to test whether the short-term outcomes of RCTs could be achieved in a context of routine care by a programme covering the whole target population (UK Colorectal Cancer Screening Pilot Group 2004; Goulard et al. 2008).

A new screening programme should be implemented in such a way that effectiveness can be evaluated. This can be achieved using individual-level randomisation into screening and control groups at the phase when the programme is new and resources and practical limitations prohibit the full coverage of the target population. This step-wise implementation, in which the target population is gradually taken into the programme as available resources expand, is both feasible and accepted when the available resources are used to their full extent.

A randomised screening design is helpful in the start-up phase when all the healthcare services and the infrastructure have not been evaluated within the screening programme, and since there cannot be certainty that the desired outcome and quality will be reached in that particular programme. In the first years of screening, an invitation scheme that gradually expands to cover more regions and age groups over the years can be used. Individuals in the control group will be offered screening later after the first years. This provides an unbiased comparison group.

A model from Finland is based on individual-level randomisation over the first six years (Malila, Anttila & Hakama 2005). For a six-year implementation phase it was expected that the number of colorectal cancer deaths will accumulate during 10 years from launching the programme in a population of around 3 million and a colorectal cancer mortality rate of approximately 15/100 000. Meanwhile, feasibility can be studied and the programme monitored with various process indicators such as attendance rates, proportion of test positives, detection rates, and positive predictive values.

A randomised screening design can also be used to assess the impact of alternative policies, such as different methods of invitation, or different target age groups. The randomised approach may also represent an acceptable and feasible alternative to assess the impact of a new screening test or to compare cost-effectiveness of different screening strategies, when a clinical randomised trial to evaluate the reduction in cancer occurrence or mortality is deemed impractical.

For other aspects relevant to implementation of screening programmes, see Sect. 2.3.1.

Recommendation

- Ideally, any new screening programme should be implemented using individual-level randomisation into screening and control groups in the phase when resources and practical limitations prohibit the full coverage of the target population **(VI - A).**[Rec 2.28]

2.6.5 Data collection and monitoring (see also Chapter 3)

2.6.5.1 Data sources

To determine whether a programme has been effective with respect to its impact on mortality and morbidity requires continuous follow-up of the target population over an extended period of time, and ascertainment and recording of the outcomes of the screening process and of the indicators of programme impact.

There is a special need to monitor performance of programmes using new tests.

The monitoring and evaluation of the programme therefore require that adequate provision be made in the planning process for the complete and accurate recording of all the relevant data. Achieving this goal is dependent on the development of comprehensive systems for documentation of the screening process, monitoring of data acquisition and quality, and accurate compilation and reporting of the results.

The information system should be designed to support the implementation of the different steps of screening, to record screening findings of each individual, to identify those detected with abnormalities, to monitor that the recommended action has been taken and to collect information about assessments and treatment.

For the purposes of impact evaluation this information should be linked to several external data sources, and legal authorisation to be able to achieve this should be secured: population registries, for estimating population coverage and to identify people in the target population in relation to their screening history; cancer or pathology registries, for cancer follow-up and for quality assurance purposes and feed-back to clinicians; and cause of death register for individuals in addition to population statistics, for assessing vital status and cause of death for final effectiveness evaluation.

2.6.5.2 How to respond to outcomes of monitoring

The design of the information system should take into account the views and data requirements of all groups involved in the screening programme. A wide range of consultation and participatory planning is important to improve programme evaluation, through common definition of data elements, indicators and standards. The programme should ensure that professionals involved in screening receive timely feedback on programme and individual performance. Rapid publication of the monitoring results is important as screening units and other actors need the information to run their activity and to implement quality assurance and training efforts. (See also Chapter 6).

In order to achieve these aims it is recommended to identify a coordination board that is responsible for regularly auditing the programme and taking necessary actions (including indications about the specific organisational changes which are necessary to meet the desired quality standards).

Recommendation

- In order to be able to evaluate effectiveness of screening, the data must be linked to several external data sources including population registries, cancer or pathology registries, and registers of the cause of death at the individual level in the target population. Therefore, legal authorisation should be put in place in order to be able to link the aforementioned data for follow-up when screening is introduced **(VI - A).**[Rec 2.29]

2.7   References

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

3

Evaluation and interpretation of screening outcomes

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Recommendations[1]

3.1 The development of comprehensive systems for documentation of the screening processes, monitoring of data acquisition and quality, and accurate compilation and reporting of results are essential to the evaluation of population screening programmes **(VI - A).**[Sect 3.1]

3.2 Detailed eligibility criteria should be predefined, based on a pre-specified protocol (see also Ch. 2, Rec. 2.4, Sect. 2.3.1.1) **(VI - B).**[Sect 3.2.1]

3.3 A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on screening performance **(VI - A).**[Sect 3.2.1]

3.4 Quality control procedures for the database should be available and run regularly to check the quality of the data and to correct data entry errors **(VI - A).**[Sect 3.2.1]

3.5 For monitoring the programme, tables presenting performance indicators should be produced at regular intervals (at least annually) by age and gender and by type of screening test using the collected data **(VI - A).**[Sect 3.2.5]

3.6 All indicators should be calculated and reported for age-gender subgroups **(VI - A).**[Sect 3.3]

3.7 Invitation coverage should be high (95%) in order to maximise screening impact **(VI - A).**[Sect 3.3.1]

3.8 A minimum uptake of 45% is acceptable **(III - A)**, but it is recommended to aim for a rate of at least 65% **(III - A).**[Sect 3.3.1]

3.9 Rates of inadequate FOBTs should remain low. These reflect the understanding of the people who are using the test and therefore the quality of the information given to the population. Less than 3% is acceptable, less than 1% is desirable (See Ch. 4, Rec. 4.21) **(III - A).**[Sect 3.3.2; 4.3.4]

3.10 High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening test or examination requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Sect 3.3.2; 3.3.3]

3.11 The proportion of screening and follow-up colonoscopies that are incomplete should be recorded separately. A completeness rate of >90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Sect 3.3.2; 3.3.3; 5.4.5.1]

3.12 A favourable stage distribution in screen-detected cancers compared to clinically diagnosed cancers should be observed. In absence of this condition a screening programme could not be effective **(I - A).**[Sect 3.3.2]

3.13 The rate of serious adverse effects should be monitored carefully **(III - A).**[Sect 3.3.2; 3.3.3]

3.14 High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(III - A).**[Sect 3.3.2; 3.3.3]

3.15 The time in days, between completion of a screening test and receipt of results by the participant should be as short as possible: acceptable standard >90% within 15 days **(VI - A).**[Sect 3.3.4]

3.16 Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (acceptable standard is >90%, desirable >95%). (See Ch. 5, Rec. 5.19) **(VI - B).**[Sect 3.3.4; 5.3.5]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

3.17   The time interval between positive FS or colonoscopy and definitive management should be minimised and in 95% of cases should be no more than 31 days (acceptable standard) (see Ch. 8, Rec. 8.2) **(VI - B).**[Sect 3.3.4; 8.2]

3.18   The evaluation of surrogate outcome measures requires rigorous data collection of colorectal cancer registrations and stage of disease in the target population. Such data should also be collected for the time period leading directly up to the introduction of a screening programme to allow trends to be analysed **(VI - A).**[Sect 3.4]

3.19   Data on interval cancers should be collected and reported **(VI - A).**[Sect 3.4.1]

3.20   Evaluation of interval cancer rates requires careful linkage of cancer registrations with screening history to allow cancers to be classified (i.e. as screen detected, interval, non-responders, other). A link with the cancer registry should be established **(VI - A).**[Sect 3.4.1]

3.1   Introduction

Evaluation and interpretation of screening outcomes are essential to recognising whether a colorectal cancer screening programme is achieving the goals for which it has been established. It is recognised that the context and logistics of screening programmes will differ by country and even by region. For example, the prior existence of a population register facilitates issuing personalised invitations, whereas the absence of such a register may lead to recruitment by open invitation. Many of these contextual differences will affect the measured outcomes.

The effectiveness of a programme is a function of the quality of its individual components. Success of the programme is measured not only by its impact on public health, but also by its organisation, implementation, and acceptability.

The organisational aspects of a screening programme, described in Chapter 2 of these Guidelines influence the evaluation and interpretation of screening outcomes. Therefore all aspects of the programme should be monitored and evaluated.

To determine whether a programme has been effective with regard to its impact on morbidity and mortality requires continuous follow-up of the target population over an extended time-frame. Therefore early-performance indicators using standard definitions, available early in the lifetime of a screening programme are essential to measure the quality of the programme and its potential longer-term impact.

A key component in the evaluation of population screening programmes is data collection. Colorectal cancer screening can be performed using various tests or techniques. Data collection necessary for evaluation can be common to all tests or specific to particular tests. The examples given in these Guidelines refer to in vitro stool tests based on detection of faecal occult blood (FOBT) that are currently the most widely used, and to endoscopic tests i.e. flexible sigmoidoscopy (FS) or colonoscopy (CS). In the text, gFOBT refers to guaiac-based FOBTs, and iFOBT to immunological FOBTs.

This chapter includes only the minimum data variables and indicators that should be collected and measured for the purposes of programme evaluation. It does not discuss quality indicators such as those used to measure endoscopist performance or patient satisfaction; a number of such indicators are described elsewhere in the Guidelines.

It should be noted that in a setting where opportunistic screening (for example by colonoscopy) has been taking place for some time, the uptake and performance of an organised programme may differ markedly from those in a setting where no such screening has been taking place. The majority of the values of the indicators described below will relate to the latter setting.

Recommendation

- The development of comprehensive systems for documentation of the screening processes, monitoring of data acquisition and quality, and accurate compilation and reporting of results are essential to the evaluation of a population screening programme (Day, Williams & Khaw 1989) **(VI - A).**[Rec 3.1]

3.2   Data items necessary for evaluation

This section describes the data items and information that must be collected, recorded and stored in order to generate the indicators, analyses and reports required for evaluation.

3.2.1   Programme conditions

Programme type

As mentioned above, the organisational aspects of a screening programme influence the evaluation and interpretation of screening outcomes. Population-based programmes are recommended because they require an infrastructure that is conducive to implementation of quality assurance and evaluation, such as through linkage of screening data and cancer registry data (Karsa et al. 2010). It is therefore important to document the type of programme (population-based or non-population-based) and to describe the sources of population data used for identification and invitation of the eligible target population (e.g. population registry). Data on screening outcomes should be linked with data from other registries in order to monitor and evaluate the programme.

Primary screening test

Currently only the faecal occult blood test (FOBT) is recommended by the EU for CRC screening. However endoscopic screening programmes with flexible sigmoidoscopy (FS) or colonoscopy (CS) as primary screening tests are currently running in a number of Member States. Given the potential impact of the type of primary screening test or tests used in a programme on the respective results and performance, the type of primary screening test should always be indicated when documenting results and reporting.

Population base

A screening programme is population based when every member of the target population in the area designated to be served by the programme is known to the programme, and when the eligible members of the target population are individually invited to participate.

The availability and reliability of target population data will depend on the existence, quality and accessibility of population registers in the region where the programme is being set up. Population registers are not always available and demographic data for identifying the target population might be obtained from various sources, e.g. census data, electoral registers, private or statutory health care registers or health insurance funds registers. The choice of the target population database for issuing invitations will depend on the completeness of the database and on the individuals or variables included, e.g. electoral registers might not include eligible foreigners or dates of birth.

A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on organisational aspects of the programme (coverage, participation) and screening performance. The data collected should respect a logical order and follow the development of the screening process (identification of person [date of birth, gender], date of invitation, date of reminder, date of test, test results, date of the examination performed during assessment, results, colonoscopy date, results, adverse effects, treatment). The location in the bowel of any detected lesions or cancers (Tumour site) should also be recorded [Rectum, sigmoid, descending colon (distal colon) transverse colon, splenic flexure, ascending colon].

Each variable should be precisely defined. All data collected for each round should be kept and updated information should not overwrite data provided during preceding rounds. All information on the

timing of events during each screening episode, including invitation history, should be recorded as calendar dates. This ensures maximal flexibility of the database for future evaluation efforts and participation in multi-centre studies. It also permits distinguishing between the first and subsequent screening episodes and between participants with different patterns of attendance (see Section 3.3).

- **Self registrations**

Self registrations are defined as eligible residents of the designated area served by the programme, who request screening but who are not identified by the target population register used to generate invitations. Their number should be reported separately.

- **Self referrals**

Self referrals are defined as people requesting screening before receipt of an invitation or outside the invited age-range. They should not be included in coverage by invitation, or in participation rate if in the relevant age range, but their number should be reported separately.

Recommendations

- Detailed eligibility criteria should be pre-defined based on a pre-specified protocol (see also Ch. 2, Rec. 2.4, Sect. 2.3.1.1) **(VI - B).**[Rec 3.2]

- A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on screening performance **(VI - A).**[Rec 3.3]

- Quality control procedures for the database should be available and run regularly to check the quality of the data and to correct any data entry errors. **(VI - A).**[Rec 3.4]

3.2.2 Invitation variables

Target population

The target population are those people of eligible age according to the programme policy residing in the area designated to be served by the screening programme.

Eligible population

The eligible population are those people in the target population who fulfil the eligibility criteria specified in the programme policy.

Invited

The invited are those members of the eligible population who have received an invitation for screening according to the programme policy/process; e.g. invited by mail, by primary care practitioner. N.B. Not all invitations sent may be received.

3.2.3 Process variables of primary screening and follow up

3.2.3.1 Process variables in screening with the faecal occult blood test (FOBT) and other in vitro tests

The following process variables are described in the context of screening with faecal occult blood testing because FOBT is the only screening test currently recommended by the EU. In principle, the same

definitions apply to other in vitro tests. It is recommended that the type of test used for screening is indicated when reporting data

- **Screened/tested**

The group of screened or tested participants are those who have used and returned an FOBT irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of tests performed.

- **Inadequate test**

An inadequate FOBT is a test returned by a participant, the results of which cannot be reliably determined (see Chapter 4). The quality is insufficient for processing and the test cannot be used for recording a result according to the programme policy.

- **Positive test**

A positive i.e. abnormal FOBT result is a result based on the last adequate test that according to the programme policy leads directly to referral to follow-up colonoscopy.

- **Referral to follow-up colonoscopy[2]**

This variable refers to participants with a positive FOBT who require an appointment for follow-up colonoscopy. Ideally all participants with positive FOBTs would be referred to follow-up colonoscopy.

3.2.3.2 Variables in endoscopic screening

The following process variables are described in the context of CRC screening in which either flexible sigmoidoscopy (FS) or colonoscopy (CS) is used as the primary screening test.

- **Screened**

The group of screened participants comprises those people who have attended the FS or CS screening examination, irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of exams performed.

- **Inadequate test**

This group comprises those participants who attended the FS or CS screening examination, the results of which could not be interpreted because of inadequate preparation, and who do not have an adequate screening FS or CS in the reporting period. In such cases a new screening examination should be performed.

- **Positive test**

A positive i.e. abnormal screening FS or CS is one resulting either directly in diagnosis of cancer or removal of an adenoma or other lesion, or in referral for further investigation according to the programme policy (see Chapters 2 and 5).

- **Referral to follow-up colonoscopy**

Included in this group are the participants with a positive screening FS or CS who require a medical appointment for follow-up colonoscopy.[3]

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[2] The process variables related to performance of follow-up colonoscopy as a result of a positive FOBT test are the same as for follow-up colonoscopy as a result of a positive FS or CS screening examination. They are therefore described in Section 3.2.3.2 ("referral to surgery or tertiary endoscopy", "severe complications requiring hospitalisation", "30-day mortality").

[3] In rare cases in which follow-up colonoscopy is not possible, other follow-up examinations may be performed. Those patients should be included in the group referred to follow-up CS but should also be counted separately.

- **Referral to surgery or tertiary endoscopy**

This group of participants includes those who require an appointment for surgery or tertiary endoscopy for removal of challenging lesions following a positive screening FS or CS (or as a consequence of follow-up colonoscopy after primary screening with FS or CS).

- **Severe complications requiring hospitalisation**

A very small number of participants will develop severe complications such as hospitalisation within 30 days due to serious haemorrhage involving transfusion, or due to perforation, vagal syndrome or peritonitis-like syndrome as a consequence of primary screening with FS or CS (or as a consequence of follow-up colonoscopy for any primary screening test).

- **30-day mortality**

In a much smaller number of participants than those experiencing severe complications requiring hospitalisation, death may occur within 30 days after having undergone primary screening with FS or CS or follow-up colonoscopy, whether diagnostic or therapeutic, for any screening test. If the death is attributed to complications caused by the endoscopy, the participant should be counted in this group.

3.2.4 Programme outcome variables

The following outcome variables apply to CRC screening performed with any of the currently available primary screening tests.

Follow-up colonoscopy

Participants in the group on which diagnostic or therapeutic colonoscopy[4] has been performed to follow-up primary screening according to programme policy include participants, the screening endoscopy of which was inadequate or incomplete. Note that each person is counted once regardless of the number of follow-up colonoscopies that were performed. Where more than one colonoscopy or other follow-up investigation is performed, the reported result should be that of the complete diagnostic or therapeutic work-up.

Definitions of what is included in the reported result (e.g. grade of neoplasia,[5] TNM stage, other lesions) are given in Chapter 7 (Sect. 7.2, Table 7.1, Rec. 7.1-7.5, 7.8).

If more than one lesion is found, then the lesion with the worst prognosis (see Chapter 7) should be indicated as the outcome of screening.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure (see Ch. 7 and Ch. 8) should be recorded.

Lesions

Any lesion removed or biopsied at endoscopy or surgery (whether or not they were diagnosed as adenomas) should be recorded.

Adenomas

Pathological specimens removed at endoscopy or surgery that have been reported by a pathologist to be adenomatous should be recorded.

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[4] See previous footnote on follow-up colonoscopy.

[5] In screening programmes the use of the term "advanced adenoma" has developed and is sometimes used to categorise adenomas for management. In the present context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component (Ch. 7).

Advanced adenoma

If it is not possible to collect such details for organisational reasons, the programme should at least focus on collecting and reporting data on adenomas ≥10 mm in size (see Ch. 9, Sect. 9.1). For definition, see Ch. 7, Sect. 7.2, and footnote 5 on previous page.

Cancers

Colorectal cancer diagnosed by the screening programme, or diagnosed as a direct result of participating in the screening programme (see Ch. 7, Sect 7.2 for definition).

Severe complications requiring hospitalisation

For definition, see Sect. 3.2.3.2.

30 day mortality

For details, see Sect. 3.2.3.2.

3.2.5   Data tables

Recommendation

- For monitoring the programme, tables presenting performance indicators should be produced at regular intervals (at least annually) by age and gender and by type of screening test using the collected data **(VI - A).**[Rec 3.5]

Tables should present data for people, not data for tests, and therefore each person is counted once regardless of the number of tests performed (see Table 3.1).

They should present the participation in the programme, the main results of testing, and the main detection outcomes. When processing the data, decisions should be made regarding age. Age can be calculated according to different events (age at invitation, age at time of screening, age at time of diagnosis). Age at time of screening is preferable for indicators pertaining to the testing procedure, results and outcome. Age should be presented in 5-year groups.

Table 3.1: List of recommended data tables to be produced by CRC screening programmes

1. Targeted

2. Eligible

3. Invited

4. Screened/tested at first screening and at subsequent screening episodes

5. Inadequate tests

6. Positive test or screening

7. Follow-up colonoscopy examination attended (diagnostic assessment and/or treatment)

8. Negative follow-up colonoscopy examination (diagnostic assessment and/or treatment)

9. Positive follow-up colonoscopy examination (diagnostic assessment and/or treatment)

10. Lesion detected (at least one)

11. Adenoma detected (at least one)

12. Non-advanced adenoma detected (at least one)

13. Advanced/high-risk adenoma detected (at least one)

14. Cancer detected by stage

Tables should record the number of people by age, sex and type of screening test in the respective reporting period. Where applicable, data should be broken down by initial and subsequent screening episodes.

3.3 Early performance indicators

Several rounds of screening are required before the impact of a screening programme on CRC mortality in the target population can be measured. Early performance indicators using standard definitions must therefore be used early in the lifetime of a screening programme to measure the quality of the screening process and to assess its potential longer-term impact. The accumulating experience in piloting and implementing population-based screening programmes provides an evidence base that can be used to establish and refine standards and set performance targets.

Factors affecting performance indicators

Coverage and uptake, i.e. participation, are organisational parameters that apply to CRC screening programmes using any kind of primary screening test. They have a substantial impact on the potential effectiveness of any screening programme because they reflect the degree to which the population is exposed to the screening intervention. Coverage and uptake in turn will be affected by the age and gender distribution of the target population due to differential uptake rates. Screening performance indicators will be affected by the age and gender distribution of the population screened due to variation in underlying incidence of disease.

Recommendation

- All indicators should be calculated and reported for age-gender subgroups **(VI - A).**[Rec 3.6]

In addition, age-gender standardised measurements should be developed for comparative purposes.

Age should be recorded as the age of the person at the time of the invitation (for measurement of coverage/participation) or at time of screening (for measurement of screening outcome) for the respective screening round. The outcome of the screening examination for a person should thus be recorded in the same age category throughout a particular screening episode.

Screening performance indicators will also be affected by the background incidence in the target population in the absence of screening. Efforts should therefore be made to document age-gender specific incidence rates in the target population for the period immediately prior to the introduction of the screening programme.

If high-risk subjects are identified, managed, and/or excluded from the programme and reported separately, this should be stated.

Performance indicators will also vary according to whether the screen is a prevalent (first) screen for those invited for the first time, an incident (repeat) screen for those previously screened at the routine interval, or a screen for previous non-responders. Indicators at subsequent rounds will vary according to the screening interval.

Only the first organised screening round will consist entirely of subjects invited and attending for the first time; all additional rounds will comprise subjects falling into each of the categories described above. The cut-off point for separating 'subsequent regular' from 'subsequent irregular' screening should be established, taking into consideration that most programmes do not succeed in inviting each individual participant at the routine screening interval (e.g. a cut-off point at 30 months for a programme with a 2-year screening interval).

Data should be analysed separately for those invited/screened at:

- initial screening, i.e. the first invitation of individual people within the screening programme, regardless of the organisational screening round;
- subsequent invitation for previous never responders;
- subsequent invitation for those previously screened[6];
- screens as a result of self-referral (defined as people requesting screening before reception of an invitation or outside the invited age range); and
- screened following self-registration (those not recorded in target population).

Tables 3.2–3.5 list the key performance indicators for gFOBT, iFOBT, FS and colonoscopy respectively that have been reported from randomised controlled trials and from population-based programmes. For the majority of indicators the published values will have been influenced by the screening policy adopted in the respective trials and programmes. Other than those related to participation, the values reported here have therefore not been used to define acceptable levels.

There are a large number of possible process indicators, reflecting specific parts of the screening process. The present outline is confined to those that have epidemiological importance as identified within the trials. They measure participation, quality, efficacy, and organisation. Except for measures of participation, all other indicators are presented separately for in vitro tests (FOBT) and for endoscopic tests (FS or colonoscopy).

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[6] Where possible, these should be separated into invitations at the routine screening interval defined by the screening policy, and subsequent invitations at irregular intervals, i.e. those who have been screened at least once who do not respond to an invitation to routine re-screening and are invited in a subsequent organisational screening round [or attend a subsequent screening more than a defined time frame after the previous test].

3.3.1 Programme coverage and uptake

Coverage and uptake, i.e. participation are organisational parameters that apply to CRC screening programmes using any kind of primary screening test.

Coverage by invitation

Coverage of the screening programme by invitation is the extent to which the invitations sent out by the screening programme within the defined screening interval include the eligible population. It gives information on the performance of the organisation of the programme in inviting the target population within the defined screening period.

$$\frac{\text{N people invited during the time frame*}}{\text{N eligible people in the target population during the time frame*}}$$

* equal to the defined screening interval or reporting period, e.g. 12 months in the case of yearly reporting.

The eligible population is defined in Ch. 2, Sect. 2.3.1.1 (inclusion/exclusion criteria).

Recommendation

- Invitation coverage should be high (95%) in order to maximise screening impact. **(VI - A).**[Rec 3.7]

Coverage by examination

Coverage of the screening programme by examination is the extent to which screening examinations have actually been delivered to the eligible population**.**

$$\frac{\text{N screened/tested during the time frame*}}{\text{N eligible people in the target population during the time frame*}}$$

* equal to the defined screening interval or reporting period

Screened here is defined as people tested at least once regardless of whether the result was adequate or inadequate and includes self referrals but not self registrations. The latter should be counted but reported separately. Coverage of the target age range for invitation will by definition exclude self referrals outside the age range. This is important in programmes where no comprehensive population lists are available and self referral or self registration can account for a large proportion of subjects screened.

Both of the coverage indicators (by invitation and examination) are useful at a local level to assess completeness of population lists and target population's database.

Uptake (participation) rate

The number of people who have been screened, within a defined time frame following an invitation, as a proportion of all people who are invited to attend for screening.

$$\frac{\text{N people invited and screened/tested during the time frame*}}{\text{N eligible people invited during the time frame*}}$$

* equal to the defined screening interval or reporting period

The effectiveness of the programme will depend on the participation rate. In the randomised FOBT trials, uptake at the first round was between 49.5% and 66.8% (Table 3.2); uptake at subsequent rounds varied according to the policy for reinvitation. In a US study that recruited volunteers 75%–78% of subjects invited were screened at least once (Mandel et al. 1993). Reported uptake in population-based programmes ranges from 17.2% to 90.1% at the first round; the range at subsequent rounds is smaller (22.3%–52.1%) (see Tables 3.2 and 3.3).

For flexible sigmoidoscopy, uptake rates in RCTs ranged from 32.4% to 83.5%, again with high rates being associated with recruitment of volunteers or those who had expressed interest in participation). In population-based programmes, uptake rates range from 7% to 55% (Table 3.4).

Recommendation

- A minimum uptake of at least 45% is acceptable **(III - A)**, but it is recommended to aim for a rate of at least 65% (Faivre et al. 1991; Zorzi et al. 2008) **(III - A).**[Rec 3.8]

3.3.2 Outcomes with faecal occult blood testing (FOBT) for primary screening

A table should be made to present the test results (positive, negative, or inadequate) by gender and age. Results should also be broken down by initial and subsequent screens as described above (Section 3.3). FOBT indicators will vary according to the type of test used and programme policy, and therefore these should be reported.

Inadequate FOBT rate

The rate of inadequate tests is defined as the proportion of people screened with one or more FOBT returned during the respective time frame (e.g. a 12-month period) none of which were adequate.

Rates of inadequate tests should remain low. They reflect, among other things, the understanding of the people who are using a test and therefore also the quality of the information provided to them.

$$\frac{\text{N people who returned only inadequate FOBTs during the time frame*}}{\text{N people tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

In population-based programmes, inadequate gFOBT rates between 0.4% and 4.5% (Table 3.2) have been reported. No data are available yet for iFOBT.

Recommendation

- An inadequate rate of FOBT less than 3% is acceptable, less than 1% is desirable (see Ch.4, Rec 4.21, Sect. 4.3.4) **(III - A).**[Rec 3.9]

Positive FOBT rate

In the RCTs of gFOBT, the positive rate without rehydration was 1.2%–3.8%, and with rehydration 1.7%–15.4%. In average risk population-based programmes the positive rate for gFOBT in participants aged 50-69 years was 1.5% – 8.5% in the first round. Only two studies have reported rates at subsequent rounds, with positive rates of 0.8% and 1.8% (Table 3.2).

$$\frac{\text{N people with a positive FOBT result during the time frame*}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

For iFOBT the range of positive rates in population-based studies was 4.4%–11.1% in the first round, with one study reporting a rate in subsequent rounds of 3.9% (Zorzi et al. 2008) (Table 3.3).

Positive test rates for gFOBT will depend on the method of slide handling used, and will be higher if the slides are rehydrated. The positive rate for iFOBT will vary according to the cut-off level adopted (see Chapter 4).

Positive rates should be presented in a table by 5–year age groups and gender. Positive rates are higher in men than in women and increase with age in both genders reflecting the natural history of the disease.

Referral to follow-up colonoscopy after FOBT

The rate of referral for follow-up colonoscopy after a positive FOBT is defined as the proportion of people screened with a positive test and referred to colonoscopy among those presenting with a positive/abnormal test during the respective time frame.

$$\frac{\text{N people presenting with a positive test and referred for colonoscopy during the time frame*}}{\text{N people presenting with a positive/abnormal test during the time frame*}}$$

* equal to the defined screening interval or reporting period

Recommendation

- High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening test or examination requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Rec 3.10]

Follow-up colonoscopy compliance rate

In the RCTs using gFOBT, colonoscopy compliance rates range from 73% to 95%; in population programmes rates between 88% and 92% have been reported. (Table 3.2)

$$\frac{\text{N people having attended a colonoscopy examination during the time frame*}}{\text{N people presenting with a positive screening test and referred during the time frame*}}$$

* equal to the defined screening interval or reporting period

Recommendation

- High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(III - A).**[Rec 3.14]

Follow-up colonoscopy outcome, detection rates

A table should be made to present colonoscopy results by gender and age:

- Negative, (defined as no identified lesions, adenomas or cancers);
- Presence of adenomas of any size;
- Presence of non-advanced adenomas;
- Presence of advanced adenomas; and
- Presence of advanced cancers.

The above colonoscopy indicators are essential programme indicators of efficacy.

Completion of follow-up colonoscopy after FOBT

The proportion of incomplete colonoscopies should be recorded (see Chapter 5 for definition). One RCT of FOB testing reported a completion rate at follow-up colonoscopy of 89% (Kronborg et al. 1996).

Recommendation

- A completion rate of follow-up colonoscopy of >90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Rec 3.11]

If more than one lesion is found, the lesion with the worst prognosis should be used for evaluation purposes as the result of follow-up colonoscopy.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure should be recorded, (see Ch. 1 and Ch. 7).

Detection rates of FOBT screening programme

- **Lesion detection rate**

The lesion detection rate is reported in % and is defined as the proportion of participants with at least one detected lesion among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected lesion during the time frame*}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Adenoma detection rate**

The adenoma detection rate is reported per 1 000 (‰) and is defined as the proportion of participants with at least one detected adenoma among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected adenoma during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Advanced adenoma detection rate**

The advanced adenoma detection rate is reported per 1 000 (‰) and is defined as the proportion of participants with at least one detected advanced adenoma among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected advanced adenoma during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Cancer detection rate**

Detection rates for cancers and adenomas observed in population-based programmes using FOBT are summarised in Table 3.2 and 3.3. Cancer detection rates range from 1.2‰ to 9.5‰ at the first round, with lower rates at subsequent rounds. Detection rates of all adenomas range from 5.2‰ to 22.3‰ at the first round, with lower rates at subsequent rounds. (However some studies report only advanced or high-risk adenomas.)

$$\frac{\text{N people with at least one detected cancer during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Stage of screen-detected cancers**

The stage distribution of screen-detected cancers should be reported by screening round, age and gender. In the RCTs using only gFOBT, the proportion of screen-detected cancers that were Dukes Stage A ranged from 26% to 36% (Table 3.2).

The staging of colon cancer should use firstly the international TNM classification and secondly the Dukes classification (see Chapter 7).

Recommendation

- A favourable stage distribution in screen-detected cancers compared to clinically diagnosed cancers should be observed. In absence of this condition a screening programme could not be effective **(I - A).**[Rec 3.12]

Positive predictive values for FOBT screening programmes

Since lesions can only be detected if follow-up colonoscopy is performed, the definitions below take into account whether or not follow-up CS was actually performed. Other positive predictive values can be calculated, such as the PPV of the positive test without any further adjustment. In this case, the denominator would be the number of people presenting with a positive test result leading to referral for colonoscopy.

- **PPV for detection of lesions**

The positive predictive value (PPV) for detection of a lesion through an FOBT screening programme is defined as the percentage of people with detection of at least one lesion at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected lesion during the time frame *}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **PPV for detection of adenoma**

The positive predictive value for detection of an adenoma through an FOBT screening programme is defined as the percentage of people with detection of at least one adenoma at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected adenoma during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **PPV for detection of advanced adenoma**

The positive predictive value for detection of an advanced adenoma through an FOBT screening programme is defined as the percentage of people with detection of at least one advanced adenoma at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected advanced adenoma advanced adenoma during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

Values varied between 14.6% and 54.5% in the RCTs using only gFOBT without rehydration and from 6.0% to 11.0% with rehydration.

- **PPV for detection of cancer**

The positive predictive value for detection of a cancer through an FOBT screening programme is defined as the percentage of people with detection of at least one cancer at follow-up CS among those with positive FOBT tests who have attended follow-up CS. Values varied between 5.2% and 18.7% in the RCTs without rehydration and from 4.5% to 8.6% in the initial round of population-based programmes (5.3% to 10.6% in subsequent screening) (Tables 3.2 and 3.3).

$$\frac{\text{N people with at least one detected cancer during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

Table 3.2: Evidence on performance indicators for guaiac based FOB testing.

	Range from RCTs[1]	Range from population-based programmes[2]
Uptake rate 1st round	49.5%–66.8%	17.2%–70.8%
Subsequent round	60%–94%	22.3%–52.1%
Inadequate rate	-	0.4%–4.5%
Positive rate for FOBT	1.2%–3.8%	1st screen 1.5%–8.5%
	(1.7%–15.4%) (with rehydration)	Subsequent screen 0.8%–1.8%
Colonoscopy compliance rate	73%[3]–95%	87.8%–91.7%
Colonoscopy completion rate	89%–100%	72%–95%
Adenoma detection rate 1st screen	5–14.5‰	5.2–10.5‰
Subsequent screen	3.8‰	3.3–4.7‰
Cancer detection rate 1st screen	1–2.5‰	1.2–2.3‰
Subsequent screen	1.1–1.4‰	0.9–0.94‰
Proportion of screen detected cancers that are stage A	26%–36%	-
PPV for adenoma as the most severe lesion	14.6%–54.8%	30.3%
	(6.0%–11.0%) (with rehydration)	26.8%
PPV for cancer	5.2%–18.7%	1st screen 6.2%–8.5%
	(0.9%–6.1%) (with rehydration)	Subsequent screen 5.3%–10.6%
Adverse effects (perforation, serious haemorrhage)	0.5%–1.6% of subjects undergoing colonoscopy	-

[1] Minnesota   (Mandel et al. 1993)   age range 50-80   annual and biennial, Hemoccult, 82.5% rehydrated.

   Goteborg   (Kewenter et al. 1994)   age range 60-64   2 screens at 16-24 month interval, Hemoccult II, majority hydrated.

   Funen   (Kronborg et al. 1996)   age range 45-75   biennial, Hemoccult II not rehydrated.

   Nottingham   (Hardcastle et al. 1996)   age range 45-74   biennial, Hemoccult not rehydrated.

   Netherlands   (Hol et al. 2010)   age range 50-74

[2] Greece   (Chrissidis et al. 2004)   age range 50+

   France   (Denis et al. 2007)   age range 50-74

   Italy   (Federici et al. 2006)   age range 50-74

   UK   (Hart et al. 2003)   age range 41-65

   Spain   (Peris et al. 2007)   age range 50-69

   UK   (Weller et al. 2007)   age range 50-69

   Finland   (Malila et al. 2008)   age range 60-69

[3] Others had an alternative such as barium enema

Table 3.3: Evidence on performance indicators for iFOB testing

		Data from RCT[1]	Range from population-based programmes[2]
Uptake (participation) rate		61.5%	17%–90.1%
Inadequate rate		-	-
Positive rate	Round 1	4.8%	4.4%–11.1%
	Any round		7.1%
	Round 2		3.9%
Colonoscopy compliance rate		96%	60%–93.1%
Colonoscopy completion rate		98%	-
Adenoma detection rate	1st screen	27.6‰	13.3–22.3‰
Cancer detection rate	1st screen	4.7‰	1.8–9.5‰
	2nd screen		1.3‰
PPV adenoma	1st screen	59.8%	19.6%–40.3%
PPV cancer	1st screen	10.2%	4.5%–8.6%
	2nd screen		4.0%

[1] Netherlands (Hol et al. 2010)   age range 50-74

[2] Italy   (Crotta et al. 2004)   age range 50-74

   Italy   (Grazzini et al. 2004)   age range 50-70

   Uruguay   (Fenocchi et al. 2006)   age range 50+

   Japan   (Saito 2006)   age range 40+

Endoscopic complications in FOBT screening programme

In addition to death within 30 days, other serious complications that may be attributable to the endoscopic examination are described in Sect. 3.2.3.2. However, many different endoscopic complications can occur in FOBT screening programmes, all complications should be recorded as well as the respective cause, if ascertainable.

For any complication the rate is defined as the proportion of participants presenting with a complication among those having attended a colonoscopy during the respective time frame. The rate should be calculated in total and separately for screening and follow-up colonoscopy if applicable.

$$\frac{\text{N people presenting with complication during the time frame*}}{\text{N people having attended a colonoscopy during the time frame *}}$$

* equal to the defined screening interval or reporting period

Recommendation

- The rate of serious adverse effects should be monitored carefully **(VI - A).**[Rec 3.13]

The RCTs in Nottingham and Minnesota showed that approximately 16 major complications due to follow-up CS occurred per 1 million persons screened with FOBT. This corresponds approximately to the risk of major complications from follow-up colonoscopy in a well-organised high-quality flexible sigmoidoscopy screening programme (see Ch. 1, Sect. 1.2.1.4 and 1.3.1.4).

3.3.3 Outcomes with flexible sigmoidoscopy (FS) or colonoscopy (CS) as primary screening tests

A table should be made to present the test results (positive, negative, or inadequate) by gender and age. Results should also be broken down by initial and subsequent screens as described above (Sect. 3.3).

Inadequate FS or CS rates

An inadequate FS or CS occurs when the examination cannot be performed because of inadequate-preparation.

In two RCTs inadequate FS rates ranged from 11% to 12.7% (Table 3.4) (Weissfeld et al. 2005; Segnan et al. 2007).

$$\frac{\text{N people with an inadequate FS or CS, respectively, during the time frame*}}{\text{N people screened with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

Complete FS or CS rates

FS and CS examinations are considered complete when conducted under adequate bowel preparation and with visualisation of the colon beyond the sigmoid-descending-colon-junction (FS), or the caecum (CS).

$$\frac{\text{N people with complete FS or CS, respectively*}}{\text{N people screened with FS or CS, respectively, under adequate bowel preparation}}$$

* equal to the defined screening interval or reporting period

One RCT has reported a rate of incomplete CS examination of 7.5% (Segnan et al. 2007). Other authors reported rates of 1.3% and 8.9% for CS (Schoenfeld et al. 2005; Regula et al. 2006). The recommended standard (unadjusted caecal intubation rate, see Ch. 5, Sect 5.4.5.1) is >90%.

Endoscopy outcome tables

A table should be made to present the screening endoscopy results by gender and age:

- Negative, (defined as no identified lesions, adenomas or cancers);
- Presence of adenomas of any size;
- Presence of non-advanced adenomas;
- Presence of advanced adenomas; and
- Presence of cancers.

A similar table should be made to present the endoscopic results of follow-up colonoscopy in participants with positive FS or CS screening exams who are referred to follow-up colonoscopy (see below).

To calculate the following detection rates, the data of the two tables should be combined. Separate analysis of screening and follow-up endoscopy is also recommended for quality assurance purposes (see below: "Follow-up colonoscopy outcome tables").

Positive FS or CS rate

The positive FS rate reported in different studies depends on the definition used (for example whether removed lesions not requiring further surveillance are recorded as a positive result or a negative result). The reported rates varied from 17.6% to 27.7% in 4 RCTs (Table 3.4). Positive CS rates ranging from 20.4% to 53.8% have been reported from population studies (Lieberman et al. 2000; Shoenfeld et al. 2005; Regula et al. 2006). The latter rate was reported in a study with a high percentage of participants with a family history of CRC.

$$\frac{\text{N people with a positive FS or CS result, respectively, during the time frame *}}{\text{N people screened with FS or CS, respectively, during the time frame *}}$$

* equal to the defined screening interval or reporting period

Detection rates of FS or CS screening programmes

- **Lesion detection rate**

The lesion detection rate is reported in % and is defined as the proportion of participants with at least one detected lesion among those adequately tested during the respective time frame.

Detection rates should be presented in a table by 5-year age groups and gender.

$$\frac{\text{N people with at least one detected lesion during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Adenoma detection rate**

The adenoma detection rate is reported in % and is defined as the proportion of participants with at least one detected adenoma among those adequately tested during the respective time period.

In the RCTs of flexible sigmoidoscopy, adenoma detection rates ranged from 8.7% to 12.1% (Table 3.4).

$$\frac{\text{N people with at least one detected adenoma during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Advanced adenoma detection rate**

The advanced adenoma detection rate is reported in % and is defined as the proportion of participants with at least one detected advanced adenoma among those adequately tested during the respective time period.

Advanced adenoma detection rates of 4.9% to 8.6% have been reported in population studies of colonoscopy (Lieberman et al. 2000; Shoenfeld et al. 2005; Regula et al 2006) (Table 3.5).

$$\frac{\text{N people with at least one detected advanced adenoma during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Cancer detection rate**

The cancer detection rate is determined as the proportion of FS or CS screening participants, respectively, with at least one detected colorectal cancer among those adequately examined during the respective time period. In the RCTs of flexible sigmoidoscopy, detection rates ranged from 2.9‰ to 5.4‰ (Table 3.4). Somewhat higher rates can be expected for screening CS due to inspection of the entire colon.

$$\frac{\text{N people with at least one detected cancer during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

Referral to follow-up colonoscopy after FS or CS

The respective rate of referral for follow-up colonoscopy after a positive screening FS or CS is defined as the proportion of people with a positive screening examination and referred to colonoscopy among those presenting with a positive/abnormal screening exam during the respective time frame and requiring follow-up CS according to the programme policy. In the RCTs of flexible sigmoidoscopy, referral rates ranged from 8.3% to 19.5% of all participants with a positive FS (Table 3.4).

N people presenting with a positive FS or CS, respectively, and referred for follow-up CS during time frame*
N people presenting with a positive/abnormal FS or CS, respectively, and requiring follow-up during the time frame*

* equal to the defined screening interval or reporting period

As a percentage of all people with a positive test result, referral rates for follow-up colonoscopy will be much higher in FOBT-based screening programmes, than in FS screening programmes, depending on the programme policy for referral after a positive screening FS. Referral for follow-up CS after screening CS will be much less common than after screening FS because most lesions found at screening can be removed during screening CS. However, as a proportion of all people referred to follow-up according to the programme policy, compliance should be high irrespective of type of primary screening test.

Recommendation

• High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening FS or CS requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Rec 3.10]

Follow-up colonoscopy compliance rate after screening FS or CS

The rate of compliance with referral to follow-up colonoscopy after a positive endoscopic screening examination is defined as the proportion of people having attended a follow-up CS during the time frame among those presenting with a positive screening FS or CS, respectively, who were referred during the time frame.

N people having attended a follow-up CS examination during the time frame*
N people presenting with a positive screening FS or CS, respectively, and referred during the time frame*

* equal to the defined screening interval or reporting period

Recommendation

• High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(VI - A).**[Rec 3.14]

Follow-up colonoscopy outcome tables

A table should be made to present colonoscopy results by gender and age:

• Negative (defined as no identified lesions, adenomas or cancer);
• Presence of adenomas of any size;
• Presence of non-advanced adenomas;
• Presence of advanced adenomas; and
• Presence of cancer.

As mentioned above, a similar table should be made to present the results of primary screening endoscopic exams. To calculate the programme detection rates of lesions, adenomas and cancers, the data of the two tables should be combined.

Completion of follow-up colonoscopy after FS or CS

The proportion of follow-up colonoscopies that are incomplete (lack of visualisation of the caecum, see Ch. 5, Sect. 5.4.5.1) should be recorded.

Recommendation

- For follow-up colonoscopy after FS or screening CS, a completion rate of 90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Rec 3.11]

If more than one lesion is found during follow-up colonoscopy, then the lesion with the worst prognosis should be used for the programme evaluation.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure should be used for the evaluation database (see Sect. 3.2.4; Ch. 7).

Endoscopic complications of FS or CS screening programmes

The endoscopic complications that can appear in CRC screening programmes using FS or CS are the same as those described above with respect to follow-up colonoscopy performed in an FOBT screening programme (see Sect. 3.3.2, p. 89).

The following complications are defined as serious: death within 30 days; or hospitalisation within 30 days due to serious haemorrhage involving transfusion, or due to perforation, vagal syndrome or peritonitis-like syndrome. All complications should be recorded as well as the respective cause, if discernible.

For any complication the rate is defined as the proportion of participants presenting with a complication among those having attended the respective type of endoscopic exam (FS or CS). Rates should be broken down by exams performed for primary screening and exams performed for follow-up of positive screening results.

$$\frac{\text{N people presenting with complication of FS or CS, respectively, during time frame*}}{\text{N people having attended the respective exam (FS or CS) during the time frame *}}$$

* equal to the defined screening interval or reporting period

In RCTs, rates of severe complications of FS have been reported at 0.02% to 0.03% (Weissfeld et al. 2005; Segnan et al. 2007). Three studies of colonoscopy screening have reported rates of severe complications of 0.0% to 0.3% (Lieberman et al. 2000; Schoenfeld et al. 2005; Regula et al. 2006). In a well-organised high-quality flexible sigmoidoscopy screening programme the risk of major complications is about 0.3%–0.5% for follow-up colonoscopy **(III)** (see also Ch. 1, Sect. 1.2.1.4 and 1.3.1.4).

Recommendation

- The rate of serious adverse effects should be carefully monitored **(VI - A).**[Rec 3.13]

Table 3.4: Evidence on performance indicators for flexible sigmoidoscopy

	Range from RCTs[1]	Range from population studies[2]
Uptake rate	32.4%–83.5%	7%–55%
Inadequate rate	11%–12.7%	-
Positive rate	10.2%–27.7%	1st round 5.4% 2nd round 3.9%
Referral rate for further investigation	8.3%–19.5%	-
Adenoma detection rate	8.7%–20.6%	14% 5yr recall 11%
Cancer detection rate	2.9‰–5.8‰	4‰ 5yr recall 0.0‰
Proportion of screen detected cancers Dukes stage A	54%–62%	69% (Stage I)
Severe complications Perforations Severe haemorrhage	0.02%–0.03% Near to 0%	-

[1] SCORE   (Segnan et al. 2002)   age range 55-64
    UKFS   (UK Flexible Sigmoidoscopy
              Screening Trial Investigators 2002)   age range 55-64
    NORCCAP   (Gondal et al. 2003)   age range 55-64
    PLCO   (Weissfeld et al. 2005)   age range 55-74
    SCORE2   (Segnan et al. 2005)   age range 55-64
    SCORE3   (Segnan et al. 2007)   age range 55-64
    Netherlands (Hol et al. 2010)   age range 50-74

[2] Italy   (Federici et al. 2006)   age range 50-74
    UK   (Brotherstone et al. 2007)   age range 60-64
    Australia   (Viiala & Olynyk 2007)   age range 55-64
    Italy   (Zorzi et al. 2008)   age range 50-69

Table 3.5: Evidence on performance indicators for screening colonoscopy

	Population studies[1]
Positive rate	20.4%–53.8%[2]
Any adenoma or cancer detection rate	14.9%–37.5%[2]
Advanced neoplasia detection rate	4.9%–10.5%
Advanced adenoma detection rate	4.9%–8.6%
Complication rate	0.0%–0.3%

[1] US   (Schoenfeld et al. 2005)   women age range 50-79

US   (Lieberman et al. 2000)   men age range 50-75

Poland   (Regula et al. 2006)   age range 50-66

[2] High percentage of participants with family history of CRC

3.3.4   Screening organisation

A number of indicators can be used to monitor the organisational performance of a screening programme.

Time interval between completion of test and receipt of results

The time interval between performing a test and receipt of results will affect patient outcomes in terms of anxiety and potentially screening outcomes in terms of stage of diagnosis of disease.

Recommendation

• The time interval between completion of test and receipt of results by the subject should be as short as possible, (acceptable standard: >90% within 15 days) **(VI - A).**[Rec 3.15]

Time interval between positive test and follow-up colonoscopy

A timely procedure is not critical in the context of primary screening but it is very important when endoscopy is performed following a previous positive screening test. A delayed procedure may not be critical biologically, but it can cause unnecessary anxiety for the screenee.

To ensure that patient anxiety is not unnecessarily increased, it is recommended that follow-up colonoscopy after positive screening be performed as soon as reasonably possible but no later than within 31 days of referral.

Recommendation

• Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (an acceptable standard is >90%, >95% is desirable). (See Ch. 5, Rec. 5.19, Sect. 5.3.5). **(VI - B).**[Rec 3.16]

Time interval between positive endoscopy (CS or FS) and start of definitive management

The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days (NHS 2007) (see Ch. 8, Rec. 8.2, Sect. 8.2).

Recommendation

* The time interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised. Acceptable standard: >90%, desirable >95% within 31 days (see Ch. 8, Rec. 8.2) **(VI - B).** [Rec 3.17]

Time interval between consecutive primary screening tests

The time interval between two consecutive primary screening tests will affect the coverage of the programme by invitation/screening.

The interval between two consecutive primary screening tests should be monitored to remain within an acceptable level (depending on the screening interval). People should be re-invited according to the date of their last test and not that of their last invitation.

If possible data pertaining to endoscopic surveillance should be monitored.
Proportion of people referred for endoscopic surveillance and proportion of people complying to endoscopic surveillance.

3.4   Long-term impact indicators

The primary objective of screening for CRC is to achieve a reduction in disease-specific mortality; in the case of FS or colonoscopy screening this will be achieved largely by a reduction in the incidence of CRC. However such a reduction in either mortality or incidence will not be discernible until many years after the introduction of the screening programme. (In some areas, opportunistic screening by colonoscopy may be widespread before the start of the programme, therefore diluting the effect of a programme). Methods for studying mortality reduction are discussed later in this chapter. In the meantime other indicators of the impact of screening on disease incidence and mortality should be monitored. These include rates of interval cancers, and surrogate outcome measures that can be used to predict the impact of screening on CRC mortality (or on the incidence of invasive disease) such as rates of overall (age-specific) incidence, stage-specific incidence rates (Denis et al. 2007).

Costs associated with all aspects of the programme should be recorded. Estimates of cost effectiveness will vary according to the health care system in the area. Costs should be monitored carefully, but comparisons between countries will be complex. (Aspects of cost-effectiveness are discussed in Chapter 1).

Finding the appropriate networking level for evaluation of incidence and mortality depends on the organisational structure of the programme. In some programmes (e.g. UK) this will be at a national level, whereas for others it will be at a regional level.

Recommendation

• Evaluation of surrogate outcome measures requires rigorous data collection of bowel cancer registrations and stage of disease in the target population. It is also preferable that such data are collected for the time period leading directly up to the introduction of a screening programme to allow trends to be analysed **(VI - A).**[Rec 3.18]

3.4.1 Interval cancers

Interval cancers are those that occur following a negative screening episode, in the interval before the next invitation to screening is due. For faecal occult blood testing interval cancers may occur following a negative FOBT, or following a positive test result with negative further assessment (colonoscopy). Rates of interval cancers reflect both the sensitivity of the screening test (false negatives), and the incidence of newly-arising cases not present at the time of screening. With increasing time since negative test, the rate and proportion of the latter will increase. In the absence of repeat screening, incidence rates would eventually reach the background level again. Rates of interval cancers should therefore be presented by time period (years) since previous screen.

For endoscopy screening and for colonoscopy follow-up of FOBT, interval cancers reflect the quality of screening as well as the sensitivity of the screening test.

Recommendation

• Data on interval cancers should be collected and reported **(VI - A).**[Rec 3.19]

Recommendation

• Evaluation of interval cancer rates requires careful linkage of cancer registrations with screening history to allow cancers to be classified (i.e. as screen detected, interval, non-responders, other). The requisite linkage must be established with the cancer registry **(VI - A).** [Rec 3.20]

Rates of interval cancers will depend on the underlying incidence in the population. They will also depend on the extent of selection bias, whereby rates in those not participating in screening differ from the general population rates. For this reason it is important that (age- and gender-specific) incidence rates in non-responders are also monitored, to allow for the underlying incidence in responders to be estimated.

Background incidence rates can be estimated from rates prior to the introduction of screening (although time trends need to be considered) or from areas not covered by the screening programme (when geographic differences need to be considered).

The interval cancer rate can therefore be expressed as a proportion of the background incidence rate, standardised for age and gender, by dividing the number of interval cancers in the specific age/gender group (I) by the ones expected based on the background incidence for that age/gender group (C), or as a proportion of the background incidence rate adjusted for non-participants (C*). The adjusted rate can be calculated as:

$$C^* = (C - (1 - P) N) / P$$

P: participation rate
N: rate in non-responders

The comparisons can be adjusted for differences in age and gender.

The rate of interval cancers in the period after a negative screening provides information on the sensitivity of the programme. The sensitivity of gFOBT-based program for detection of cancer has been estimated as 55%–57% using this method. In the Nottingham trial the estimate was based on overall

rates of interval cancers of 0.64 per 1000 person-years in the two year period after screening (Moss et al. 1999). Using the same method, the sensitivity of iFOBT-based programme has been reported as 82% (Zappa et al. 2001).

No data are available yet on the sensitivity of FS or colonoscopy-based programmes.

3.4.2 CRC incidence rates

Immediately following the introduction of a screening programme, incidence rates in the target age range should increase due to the detection of prevalent disease by screening. At re-screening, rates should return to background level apart from the advancement of the age of diagnosis by screening.

Age- and gender-specific incidence rates should therefore be reported over time. FS screening should eventually lead to a reduction in incidence rates due to detection and removal of adenomas of the distal colon, but as discussed above this is a long-term effect. Screening FOBT may also have an eventual impact in reducing incidence rates, but the effect will be less due to lower detection rates of adenomas.

Cumulative incidence rates or proxies should be used to monitor potential over-diagnosis of cancer that is cancer that would not otherwise appear during the lifetime of the individual.

3.4.3 Rates of advanced-stage disease

Screening (both FOBT and FS) should result in a reduction in the overall population incidence of late stage disease (DUKES C & D) prior to any reduction in mortality and can therefore be used as an early indicator of effectiveness. Because screening will result in the detection of a large number of early stage cases, and hence a reduction in the proportion of late stage disease, it is preferable to monitor rates of late stage disease. The ability to do this will depend on the completeness of stage information that ideally should be available for a sufficiently lengthy period immediately prior to the introduction of the screening programme, to allow trends to be studied.

Projected mortality based on stage-adjusted cancer incidence.

Models have been developed to use prognostic information provided by Dukes stage and age at diagnosis to predict cancer mortality.

3.4.4 CRC mortality rates

As discussed above, it will be several years before the impact of population screening on CRC mortality becomes observable, and many more years before the full effect is achieved. The timing of a reduction depends on the natural history of the disease, and the 'lead time' due to screening (i.e. the time by which screening advances the date of diagnosis) as well as on the time taken to cover the target population. It will also depend on the quality of screening.

Methods to evaluate the impact of screening on CRC mortality include analyses of population trends, cohort studies (aggregated or individual-based) and case-control studies.

Population trends

Mortality from CRC has been decreasing in many European countries since the mid 1990's, (Karim-Kos et al. 2008). Analyses of the routinely produced age-gender specific population rates over time will be subject to limitations due to the dilution of the effect of screening from deaths occurring in cases diagnosed prior to the introduction of screening, and/or at an age below which invitations begin. This can be overcome by use of refined CRC mortality rates in which such deaths are excluded. However, the rates will also be confounded by other factors such as cohort effects on underlying incidence, and by the effects of improvements in treatment and/or the stage of diagnosis of symptomatic disease on survival and mortality. Thus whilst a lack of any reduction in population mortality rates several years after the introduction of a screening programme should be a cause for concern, it is difficult to use such trends to quantify the effect, and attempts to do so should take account of the factors discussed above.

Cohort studies

In some settings, the introduction of population screening will have been phased in such a way as to facilitate comparisons of populations invited at different time points. Such a model has been used in Finland (see Ch. 2, Sect. 2.6.4). In the absence of such a system, comparisons can be made between geographical areas (regions invited/not invited to screening) or between the same population in different time periods before and after the introduction of screening. Both types of comparison are liable to possible bias due to underlying differences in the risk in the populations/time-periods. This may – under certain circumstances – be compensated for by including also a comparison group from geographic areas where no invitational program existed from before the introduction of screening. Cohort studies using aggregated data need estimates of incidence in order to avoid dilution effect discussed above.

These biases can be avoided by individual-based cohort studies in which deaths and cancer registrations are linked to screening histories.

Case-control studies

Case control studies that compare 'exposure' (i.e. 'screening') between cases (deaths from CRC) and controls are an attractive alternative to cohort studies in terms of cost and effort. However, careful consideration of the design issues is necessary to avoid a number of potential biases, (Hosek, Flanders & Sasco 1996). The major problem with such studies is that of selection bias, due to different levels of underlying risk in participants and non-participants with screening. Methods to adjust for this are required both to estimate the mortality benefit in those actually screened, and the 'impact' on the population invited for screening.

3.5   References

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

4

Faecal Occult Blood Testing

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Recommendations[1]

Guaiac-based faecal occult blood tests

4.1   Guaiac-based faecal occult blood tests have proven characteristics that make them suitable for population screening. They lack the analytical specificity and sensitivity of immunochemical tests, their analysis cannot be automated and the concentration at which they turn from negative to positive cannot be adjusted by the user. For these reasons guaiac-based tests are not the preferred test for a modern population screening programme, although depending on local labour costs, the mechanism of kit distribution and collection and reduced sample stability in immunochemical testing, they might prove more practicable and affordable than immunochemical testing **(I - B).**[Sect 4.2.4; 4.2.7; 4.3; 4.4.2]

Immunochemical faecal occult blood tests

4.2   Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests. They are analytically and clinically more sensitive and specific, their measurement can be automated and the user can adjust the concentration at which a positive result is reported. Immunochemical tests are currently the test of choice for population screening; however, individual device characteristics including, ease of use by the participant and laboratory, suitability for transport, sampling reproducibility and sample stability are all important when selecting the iFOBT most appropriate for an individual screening programme **(II - A).**[Sect 4.2.5; 4.2.7; 4.3; 4.4.2]

DNA and other related new markers

4.3   Only tests for blood in faeces have been demonstrated to have the necessary characteristics to be suitable for population screening. DNA and other related new markers are currently unsuitable for screening, either singly or as members of a panel of tests **(III - D).**[Sect 4.2.6; 4.2.7]

Sample stability between collection and analysis

4.4   Whilst a maximum period of 14 days between collection and analysis is quoted for many guaiac faecal occult blood tests, that quoted for immunochemical tests is significantly shorter. Until more stability data are published, screening programmes should adopt the conditions and period of storage described in manufacturer's Instructions for Use having determined that they are appropriate for local conditions which might expose samples to high temperatures for long periods of time **(III - A).**[Sect 4.3.3.2; 4.3.4]

Screening algorithm:

- **Sample and test numbers**

4.5   Few studies have examined the number of stool specimens necessary to optimise the diagnostic performance of FOBT. Consideration should be given to using more than one specimen together with criteria for assigning positivity which together provide a referral rate that is clinically, logistically and financially appropriate to the screening programme. The clinical sensitivity and specificity of testing can be modified depending on how the test data are used. Guaiac-based tests typically use 3 stools, but an algorithm using additional tests can be used to adjust clinical sensitivity and specificity **(III - C).**[Sect 4.4.3.2; 4.4.3.1; 4.4.4]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

- **Determining test positivity**

4.6   The choice of a cut-off concentration to be used in an immunochemical test to discriminate between a positive and negative result will depend on the test device chosen, the number of samples used and the algorithm adopted to integrate the individual test results. Whilst an increasing number of studies are reporting the experience of different algorithms, local conditions, including the effect on sample stability of transport conditions, preclude a simple prescribed algorithm at this time. Adoption of a test device and the selection of a cut-off concentration should follow a local pilot study to ensure that the chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable **(VI - A).**^{Sect 4.4.3.1; 4.4.3.2; 4.4.4}

Test interference:

- **Dietary restriction**

4.7   Dietary constituents present potential interference in guaiac faecal occult blood tests. Dietary restriction has not been demonstrated to significantly increase screening specificity, and risks reducing participation rate. The potential for dietary interference is significantly less for immunochemical tests. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported, dietary restriction is not indicated for programmes using either guaiac-based or immunochemical tests **(II - D).**^{Sect 4.3.2.1; 4.3.2.3; 4.3.4}

- **Drug restriction**

4.8   Interference from bleeding associated with drugs such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants (e.g. warfarin) present potential interference in both guaiac and immunochemical faecal occult blood tests. Although the literature carries some contradicting reports of the effect of anticoagulants on screening outcome, drug restriction is not recommended for population screening programmes using either guaiac-based or immunochemical tests **(III - D).**^{Sect 4.3.2.2; 4.3.2.3; 4.3.4}

Faecal sampling/collection system

4.9   Many factors influence the uptake and reliability of sample collection. Inappropriate implementation can result in grossly misleading results. No single collection methodology is supported by the literature; however, the following factors should be considered when selecting a device for taking samples in population screening:

- The distribution process should be reliable and reach all selected subjects.

- The laboratory should be able to unambiguously identify the subject ID on the test device perhaps using a suitable barcode.

- The laboratory should be able to check the manufacturer's device expiry date on each returned device.

- The instructions for using the device must be simple and clear.

- The device should to be simple and easy to use by the target population.

- The device should leave minimal opportunity for collection error.

- The device should facilitate consistency in the volume of sample collected.

- The device/instructions should discourage inappropriate repeat sampling into/onto the sample device.

- Misuse of the device by participants should not cause loss of sample buffer.

- The system should not be susceptible to interference from toilet bowl disinfectants, etc.

- The screening participant should be able to record the date of sample collection to ensure the laboratory can verify receipt within an acceptable sample stability period.

- The process used by the subject for returning the device should be simple, reliable, safe and, when appropriate, should meet EU postal regulations.

A local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable **(VI - A).**^{Sect 4.2.3; 4.2.4; 4.3.2.1; 4.3.3.4; 4.3.4}

Laboratory organisation:

- **Number of laboratory sites**

4.10 Population screening necessitates the receipt, measurement and recording of thousands of tests each day. The samples should be analysed without delay to avoid further sample denaturation and avoid an increase in false negative results. Inter-laboratory analytical imprecision is well described and can be observed through established external quality assurance schemes. Improved consistency is achieved by adopting common analytical platforms, analytical and quality standards and shared staff training. The analysis needs to be reproducible across a screening population and therefore the number of analytical centres should be minimised with automated analytical systems utilised wherever possible and agreed common testing procedures adopted by each centre **(VI - B).**^{Sect 4.3.3.4; 4.3.4}

- **Laboratory staff**

4.11 All laboratories providing population screening should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and with clinical quality assurance procedures **(VI - B).**^{Sect 4.3.3.4; 4.3.4}

- **Laboratory accreditation and quality monitoring**

4.12 All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 *Medical laboratories - Particular requirements for quality and competence*. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS) **(VI - B).**^{Sect 4.3.3.4}

- **Distribution of FOBT kits by mail**

4.13 Distribution and receipt of FOBT kits using local postal services can be an effective means of reaching the designated population (Ch. 2, Rec. 2.14) **(II - B).** ^{Sect 2.5.1.1; 4.2.1; 4.3.3.4}

Maximisation of uptake – Influencing factors associated with the test kit

4.14 The choice of the test kit must be influenced by factors that enhance accessibility and uptake (see below and Ch. 2, Rec. 2.14) **(II - A):**^{Sect 4.2.3; 4.2.4; 4.4.4}

- **Dietary restrictions**

  In order to enhance participation in screening, test kits should not require dietary restrictions (Ch. 2, Rec. 2.17) **(II - A)**.^{Sect 4.3.2.1; 4.3.2.3; 4.4.4; 2.5.1.2}

- **Kit design**

  The design of a test kit should make it acceptable to the target population (see Ch. 2, Rec. 2.14) **(II - A)**.^{Sect 4.2.3; 4.2.4; 4.4.4; 2.5.1.1}

- **Simple and clear instructions**

  A clear and simple instruction sheet should be provided with the test kit (Ch. 2, Rec. 2.16) **(V - A).**^{Sect 4.2.3; 4.2.4; 4.4.4; 2.5.1.1}

Identification of participants and test results

4.15 Automated check protocols should be implemented to ensure correct identification of the screened population and complete and accurate recording of individual screening participation and test results (see Ch. 2, Rec. 2.18) **(VI - A).**^{Sect 4.3.4; 2.5.1.3}

Classification of test results

4.16 Protocols should be implemented to ensure standardised and reliable classification of the test results (Ch. 2, Rec 2.19) **(VI - A).**Sect 4.3.4; 2.5.1.3

Quality Assurance:

- **Quality assurance of gFOBT testing**

4.17 Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures. To minimise variability and error associated with visual test reading, including manual results input, the following procedures should be considered **(VI - B):**Sect 4.3.3.4; 4.3.4

  o Use of appropriate temperature for artificial lighting and neutral-coloured walls in the reading laboratory;

  o Use of a national laboratory training programme to prosper consistency of interpretation;

  o A blinded internal QC check each day for each analyst prior to commencing testing;

  o Adoption of a monitoring programme to identify operator related analytical performance (e.g. positivity variability and bias); and

  o Double entry of test results

- **Quality assurance of iFOBT testing**

4.18 Consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures **(VI - B).**Sect 4.3.3.4; 4.3.4

- **External quality assessment**

4.19 A European external quality assessment scheme should be developed to facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening **(III - B).**Sect 4.3.3.4; 4.3.4

- **Outcome monitoring**

4.20 All aspects of laboratory performance in respect of the screening test should be part of a rigorous quality assurance system. Uptake, undelivered mail, time from collection to analysis, analytical performance (internal QC and external QA), positivity rates, lost & spoilt kits and technical failure rate, technician performance variability and bias should each be subject to rigorous monitoring **(VI - A).**Sect 4.3.3.4; 4.3.4

- **Quality of information**

4.21 The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (see Ch. 3, Rec. 3.9) **(III - A).**Sect 4.3.4; 3.3.2

4.1   Introduction

The ideal biochemical test for population-screening of colorectal cancer would use a biomarker, specific and sensitive for both cancer and pre-cancer, on an easily collected sample, which could be safely and cheaply transported to a centralised laboratory for accurate, reproducible, and cheap automated analysis. None of the currently available tests fully meet all of those criteria.

That colorectal cancers and adenomatous polyps bleed, be it to varying degrees and perhaps intermittently, has provided faecal blood haemoglobin as the biomarker of choice for current screening programmes. The presence of blood in faeces can be due to pathological conditions other than neoplasia, from physiological blood loss of between 0.5 and 1.0 mL/d (Moore, Derry & McQuay 2008), from vigorous brushing of gums and from dietary constituents such as meat and meat products (Fludger et al. 2002).

The cheapest but least specific means of detecting haemoglobin uses guaiac gum, is often referred to as the guaiac Faecal Occult Blood Test or gFOBT, and its efficacy as a colorectal cancer screening test has been demonstrated in three randomised controlled trials (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996). The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs provide little specificity for lesions of the distal intestinal tract and cannot distinguish between human blood and blood residues from the diet.

The analytical sensitivity of gFOBTs to haemoglobin can be increased by hydrating the sample prior to analysis; however this brings little benefit because increased clinical sensitivity is accompanied by decreased clinical specificity. More subtle adjustment to the analytical sensitivity of gFOBTs is not technically possible, and screening programmes must configure their programme algorithm (the required number of stool samples and the required number of positive test spots) and secondary investigations, usually colonoscopy, to meet the gFOBT positivity rate.

A significant technical enhancement to the simple guaiac test for blood is achieved by using an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin. These immunochemical techniques use specific antibodies and are well-established and ubiquitous in clinical laboratories. At the point-of-care, immunochemical tests have been widely adopted, notably in fertility, pregnancy and drug tests.

Whilst the haem component of blood is common to all species, globin is conveniently species specific, so immunochemical Faecal Occult Blood tests, frequently referred to as iFOBT or FIT should not be subject to interference from dietary blood. Detection of globin also confers the advantage of making the test more specific to bleeding from the distal gastrointestinal tract, since protease enzymes gradually digest blood from the proximal tract during its passage through the intestine, rendering it less likely to be recognised by the antibodies used in an iFOBT.

Immunochemical technology enables detection of blood at lower concentrations than gFOBTs and therefore increases clinical sensitivity by detecting smaller blood losses from small or intermittently bleeding lesions. Whilst improved analytical specificity reduces false positive tests from dietary blood, their increased analytical sensitivity means that small losses from inflammatory diseases or physiological sources will bring new false positives with a higher positivity rate and decreased specificity. Several newer iFOBTs have the ability to adjust and set the cut-off concentration above which the device will report a positive result. These adjustments are made on an instrument reader, and such instruments can provide the additional and important opportunity of automating the process. Examples of products with these characteristics are the OC-Sensor Diana, *Eiken Chemical Co., Tokyo, Japan*, and the SENTiFOB, *Sentinel Diagnostics SpA, Milan, Italy*.

Population screening for colorectal cancer can now benefit from tests that have an adjustable detection limit and have the efficiencies and analytical reproducibility facilitated through automated analysis; currently only iFOBT provides this opportunity.

4.2 Biochemical tests for colorectal cancer

4.2.1 Characteristics of a test for population-screening of colorectal cancer

The list below summarises the analytical and clinical aspects of biomarker testing that make it suitable for population screening and identifies characteristics that are important for effective and efficient implementation.

Testing Process
  a. Sample
      i. Reliable sample collection, reproducible sample size
      ii. Sample collection process is simple requiring minimal contact with the stool
      iii. Safe and acceptable for the chosen method of transport, meets EU mail regulations

  b. Biomarker (analyte)
      i. Sufficiently stable, at ambient temperature, between sample collection and testing
      ii. Analytical sensitivity and specificity
          1. Adequate analytical sensitivity and specificity
          2. Adequate discrimination between neoplastic colorectal pathology and other pathologies or physiological sources of the biomarker
          3. Minimal analytical or biological interference (e.g. diet and drugs)
      iii. Ability to adjust sensitivity (and specificity) to be clinically and practically acceptable

  c. Analysis
      i. Easy and reliable to measure
      ii. Amenable to automation
      iii. Acceptably reproducible
      iv. Amenable to quality control and assessment monitoring

  d. Availability of test
      i. Reliable commercial source, long-term quality provider
      ii. Acceptable inter and intra-batch reproducibility
      iii. Affordable

Clinical Outcome
  a. Acceptable clinical performance
      i. Sensitivity
      ii. Specificity
      iii. Positive predictive value

The outcome of a screening test must be the identification of an acceptable proportion of the population who have early-stage colorectal cancer or adenoma and are amenable to successful treatment (Wilson & Jungner 1968). The screening test must also show adequate discrimination between those who have the disease and those who do not. Critically, the clinical sensitivity and specificity of the test and the way it is implemented must only identify that number of participants which is logistically and financially acceptable for referral to colonoscopy clinics.

When interpreting the clinical sensitivity and specificity of tests described in the literature, it is important to do so in the specific context of the study, the method of implementation, the nature of the population served and other local health and social welfare issues.

4.2.2 Faecal blood loss

An abnormal increase in blood loss into the intestine is necessary for the success of gFOBTs and iFOBTs. Faecal haem, haem-derived porphyrin and 51-chromium-labelled red cells have all been used to determine physiological blood loss. A recent systematic review by Moore, Derry & McQuay (2008) of the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on blood loss showed a normal daily loss in 1000 participants of less than 1 mL/d. Blood losses greater than 1 mL/d may be seen following vigorous brushing of teeth and gums, and in irritation and inflammation of the intestinal tract. Most NSAIDs, and aspirin in low doses, produce an increased blood loss of 1 to 2 mL/d which increases to 5 mL/d in 5% and 10 mL/d or more in 1% of those taking larger doses. Large daily aspirin doses of 1800 mg or more, cause daily blood losses of between 5 mL/d and 10 mL/d. Other chronic inflammatory conditions of the gastrointestinal tract including inflammatory bowel disease, colitis, Crohns' disease and perianal lesions also increase blood loss.

Macrae & St John (1982) showed the close relationship between adenoma size and blood loss using 51-chromium-labelled red cells. Levi et al. (2007) used the iFOBT OC-Sensor to show increasing faecal haemoglobin from normal and hyperplastic polyps through non-advanced and advanced polyps to cancer, with a wide spread of concentrations within each category. Fraser et al. (2008) demonstrated a clear relationship between increasing faecal blood concentration, measured with the FOB Gold iFOBT, and pathological change in 375 fresh samples from participants of the Scottish population. Ciatto et al. (2007) used the iFOBT OC-Sensor and a population that included 191 cancers and 890 adenomas detected at colonoscopy to show increasing faecal haemoglobin concentration with increasing lesion severity and size. It remains a matter of conjecture whether all early-stage cancers bleed and whether they bleed intermittently, dependant perhaps upon on the mechanics of the gastrointestinal tract and the passage of digested foodstuffs. Intermittent or variable blood loss partially explains why the less-sensitive guaiac tests do not show consistently positive tests results in patients who are later diagnosed with colorectal cancer and why, even with highly sensitive tests, 100% clinical sensitivity is not achieved.

4.2.3 Sample collection for Faecal Occult Blood Test devices

Effective sample collection is critical to the success of a screening programme. The process of collection needs to be as simple as possible. Participants will always find the process inconvenient and unpleasant. Clear, simple and practical instructions are very important both to encourage participation and to the collection of a satisfactory specimen. The easier it is to present the stool for sampling and to transfer it to the test device, the greater the likely uptake to a screening programme. Current test kits use cardboard and wooden spatulas, plastic probes with serrated ends and brushes. Whilst most kits require the sample to remain away from the water in the toilet bowl prior to sampling, other devices sample the water that surrounds the stool. Many systems accept samples taken from toilet tissue paper. One RCT (Cole et al. 2003) showed that different sampling techniques can change FOBT screening compliance and two cross-sectional studies (Greenwald 2006; Ellis et al. 2007) reported information on preference among different type of stool sampling methods. Practical experience has shown that in the age group commonly screened, physical and mental disabilities present a further reason for non-participation. Difficult sampling procedures with complex instructions greatly aggravate the inherent difficulties in collecting faecal samples.

Effective sampling is also important to the reliability of the test. Whilst the composition of faecal samples is affected by intestinal transit time, stool consistency (Rosenfield et al. 1979), undigested foodstuffs, variable sample volume will also add to poor test performance. A technique which enables the sample to reflect blood throughout the stool is preferable and so a probe which can be inserted into various parts of the stool or a spatula or brush which enables collection of material across a large surface area must be better than single point sampling (Cole et al. 2003; Young et al. 2003; Smith et al. 2006). A well-designed RCT conducted in Australia on 1818 urban residents, aged 50-69 years, compared the participation rate of three screening cohorts (Cole et al. 2003). The invited population used a wooden spatula (Hemoccult SENSA *Beckman Coulter Inc. Fullerton, CA, USA*), a spatula (FlexSure OBT *Beckman Coulter Inc. Fullerton, CA, USA*, three samples), and a brush (InSure *Enterix Inc., Edison, New Jersey, USA*, two samples) for sample collection. The overall participation rate was significantly higher in the InSure group (Hemoccult SENSA: 23.4%, FlexSure: 30.5%, InSure: 39.6% $\chi2=37.1$, p<0.00001). In a UK cross-sectional study (Ellis et al. 2007) 1318 (50%) of the eligible population (n = 2639) registered with two general practices were randomly selected and sent a three page questionnaire to determine the acceptability of three methods of FOBT sampling, a sterile long stick transport swab, a conventional smear card with short wooden applicator and a scoop with collection pot. The swab was found most preferable and the smear-card the least preferred method of collection. A small cross-sectional study (Greenwald 2006) compared toilet tissue and the short wooden applicator with the Hemoccult test but failed to show a statistical difference (p=0.05).

When applying a sample to the test device, consistent application of the required volume is important. Doubling the sample volume can double the analytical sensitivity and halving it will halve analytical sensitivity. The thickness of the card surrounding the sample collection window on a guaiac test kit is important since it will influence the volume of sample transferred onto the window. A probe that, after collection, has to pass through a small hole to wipe off sample excess is an elegant system that is used in the Hem-SP, OC-Sensor and FOB Gold iFOBT, the latter two having devices which make use of a serrated probe. This collection method is only used for immunochemical devices and the probe surface, the number and depth of the groves in the serrated probe and the size of the hole through which the probe is inserted will affect the sample volume added to the buffer in the collection tube. Stool consistency will alter the volume of sample which adheres to the groves in the probe. Poor manufacturing tolerance will also contribute to a reduction in reproducibility of the sampling system.

4.2.4 Guaiac Faecal Occult Blood Test - gFOBT

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. The method exploits the pseudoperoxidase properties of the haem moiety in haemoglobin and liberates oxygen from 3–5% dilutions of hydrogen peroxide in ethanol or methanol. The released nascent oxygen then reacts with alpha guaiaconic acid, the phenolic compound (2,5-di-(4-hydroxy-3-methoxyphenyl)-3,4-dimethylfuran) present in guaiac, a resin extracted from a hardwood tree guaiacum officinale (lignum vitae). The reaction produces a compound with a quinine structure that rearranges by two-fold electron transfer to produce an unstable blue bis-methylene quinone dye.

Guaiac is still manufactured by extraction from tree resin and is therefore susceptible to batch variation. Batch variation is potentially a significant problem for population screening programmes for which a small change in analytical sensitivity could markedly change the referral rate for colonoscopy.

Guaiacum officinale is a tree native to South America and the Caribbean and is subject to Appendix 2 of the Convention on International Trade in Endangered Species (CITES) (Keong 2009). This is an international agreement regulating trade in endangered species in order to protect them from exploitation and extinction. Under CITES, export of specimens is subject to a government-issued permit certifying that they are legally obtained and that export will not be detrimental to the survival of the species.

In all current guaiac-based devices, the guaiac is absorbed into filter paper contained within a card-board support. Faeces is applied by the participant to one side of the filter paper and, on receipt of the card, the laboratory applies an alcoholic solution of hydrogen peroxide to the other side of the paper. The volume of hydrogen peroxide added is not critical but the quantity of faeces applied is. The mass of the faecal sample will be influenced by the size of the application window and the thick-ness of the cardboard surrounding it. The hydrogen peroxide is usually applied from a dropper bottle and the laboratory staff look for the development of a blue colour within a time window prescribed by the kit manufacturer, typically 30–60 seconds. The blue dye is unstable and late reading will result in false negative results.

The test kit should have a means of checking performance; many kits will have a test positive and test negative quality control strip that develops alongside the participant's results and can highlight gross product or user errors. This QC strip should extend across the area used for clinical testing to enable identification of incomplete application of guaiac to the filter paper during product manufacture.

Good kit design can greatly facilitate proper use. The identity of the card and participant should be easily and uniquely identified by the laboratory, usually by way of a barcode. Instructions and direc-tions must be clear so that the sample is applied to the correct window. The design of the sample applicator needs to facilitate easy sample transfer and be suitable for the particular design of the kit. The size of the test window and the applicator must match to minimise marked under- or over-appli-cation of the sample. The device should carry the date the sample was applied so that the laboratory can disregard specimens that are too old to give reliable results.

Guaiac tests typically have an analytical sensitivity (limit of detection) of between 0.3 and 1 mg Hb/g of faeces, but this will be affected by the sample loading levels and the time between collection and testing. The guaiac test can be made more sensitive (0.15 mg Hb/g) by hydrating the sample on the test kit prior to adding hydrogen peroxide; that is the principal use in the Hemoccult Sensa, *Beckman Coulter Inc. Fullerton, CA, USA*.

4.2.5   Immunochemical tests - iFOBTs

Unlike gFOBT, the utility of immunochemical faecal occult blood tests (iFOBTs) has only been demon-strated in one randomised controlled trial (van Rossum et al. 2008); however the analytical superiority of immunochemical tests mean that they have recently become the test of choice for colorectal cancer screening programmes. iFOBTs have been used for population screening in Japan since 1992 (Saito 2007), and the OC-Sensor was approved for use in the U.S. by the Food and Drugs Administration (FDA) in 2001. Immunochemical tests can use monoclonal or polyclonal antibodies raised against human globin, the protein component of haemoglobin. The antibodies are attached to a latex particle, dye or an enzyme that in the presence of human globin forms a complex that can be detected by turbidity, aggregation (latex agglutination, haem-agglutination and colloidal gold agglutination) or coloured dye produced by an enzyme. Since the protein structure of human globin is unique to humans, the immunochemical test should not be subject to interference from animal blood in the diet. Unlike haem, proteolytic enzymes gradually degrade globin as it moves through the intestine, and this confers on it more specificity for pathology in the distal intestinal tract than does haem. A variation of the immunochemical test marketed by *Chemicon Europe Ltd,* MonoHaem, uses antibodies against human globin to specifically immobilise haemoglobin and then the guaiac reaction to detect the haem.

iFOBTs are typically 10-fold more expensive than gFOBTs (Fraser 2008). Increased iFOBT test kit cost can be offset by the use of automated analysers and thus reduced staff costs and, where multiple gFOBT test cards are in use, by using a single iFOBT because adequate clinical sensitivity and specificity can be obtained using a single iFOBT.

Immunochemical tests confer increased analytical specificity for human haemoglobin, and by using sensitive detection systems, they increase test sensitivity to low blood concentrations. iFOBT's typically have limits of detection of less than 0.2 mg/g stool and can detect as little as 0.3 mL of blood added to a stool sample (Saito 1996).

Immunochemical FOBTs provide opportunities for improved population screening. Hem-SP, OC-Sensor and FOB Gold all use spectrophotometric measurement systems, sometimes with charged coupled devices (CCD), to measure the degree of agglutination, turbidity or the colour generated by the test. Automating instrument measurement increases test throughput and measurement precision, and eliminates user bias (Fraser et al. 2008). Instrumentation also provides an opportunity to manually adjust the cut-off limit below which the test is reported as negative and not referred for prospective colonoscopy.

Whilst the measurements performed on the buffered faecal sample using automated analysers can be quantitative, the impossibility of providing a reproducible sample means that these systems must not be considered capable of providing reliable quantitative test results. The gFOBT and iFOBT must both be considered at semi-quantitative although the immunochemical test is analytically superior.

4.2.6   Other tests

o-Toluidine and benzidine have both been used as alternatives to guaiac but have been discontinued because they have been shown to be to be carcinogenic (IARC 2010). Imipramine and desipramine have also been described as alternative reagents to guaiac and have reports of less interference from vegetable peroxidases, iron and vitamin C, but they have not gained a place in the market (Syed, Khatoon & Silwadi 2001). Alpha guaiaconic acid, the active component of guaiac gum, has been synthesised but proved unstable and unsuitable as an alternative to the tree extract, which may contain contaminants with stabilising properties.

The measurement of porphyrins produced by the action of intestinal bacteria on haemoglobin provides an alternative method for measuring blood in faeces (Schwartz 1983; Ahlquist et al. 1984; Ahlquist et al. 1985) and recently mass spectrophotometric methods have been described, but they are unlikely to be adopted for population screening.

The literature describes many alternative biomarkers for the presence of colorectal cancer. These markers includes albumin, haptoglobin, transferrin, pyruvate kinase isoenzyme type M2, calprotectin, Ca3 anaphylotoxin, colon-specific antigen (CCSA-3 and CCSA-4) and a variety of DNA-related markers.

PK isoenzyme type M2 has shown poor sensitivity and specificity when used alongside two immuno-chemical devices (Mulder et al. 2007). Calprotectin has a role in identifying patients with inflammatory bowel disease, but a meta-analysis of the literature in 2006 concluded that it was unsuitable for screening for colorectal cancer (von Roon et al. 2007).

The use of molecular biology techniques to identify cancer-related DNA or protein biomarkers, used singly or as a panel, shows promise but is in its infancy. The use of DNA microarrays to detect the present of mutations in genes such as TP53, K-ras, APC, BAT-26 and BRAF might bring us closer to earlier detection. A study of 5486 asymptomatic patients by Imperiale in 2004 showed increased sensitivity and specificity for invasive cancer and advanced neoplasia using faecal DNA relative to gFOBT, but failed to detect over 50% in each group (Imperiale et al. 2004). A recent paper by Wang & Tang (2008) showed the hypermethylated SFRP2 gene in faecal DNA to be a candidate colorectal biomarker, but none of these DNA related markers have been demonstrated to have the necessary characteristics to qualify them for use in population screening. In Young's review of new screening tests he remarks that the epigenetic marker for the methylated vimentin gene has improved sensitivity

for cancer but that its overall performance relative to existing gFOBT and iFOBT remains unclear (Chen et al. 2005; Young & Cole 2007). In a 2008 review of the cost-effectiveness of faecal DNA, immunochemical and guaiac-based tests using the Markov model, the authors conclude that blood markers remain the preferred option in high-adherence populations (Parekh, Fendrick & Ladabaum 2008). A MEDLINE review of new stool-based tests by Haug concluded that "while promising performance characteristics have been reported for some tests, more persuasive evidence from larger, prospectively designed studies... was needed" (Haug & Brenner 2005). Currently the new markers are both expensive and show very poor sensitivity to cancer and adenomas.

In the short term, marker tests based on gene or epigenetic mutations may show merit for use in screening selected high-risk populations or for monitoring disease progression or recurrence, but in the long term we may see them as the preferred markers for general population screening.

4.2.7   Recommendations

Guaiac-based faecal occult blood tests

Guaiac-based faecal occult blood tests have proven characteristics that make them suitable for population screening. They lack the analytical specificity and sensitivity of immunochemical tests, their analysis cannot be automated and the concentration at which they turn from negative to positive cannot be adjusted by the user. For these reasons guaiac-based tests are not the preferred test for a modern population screening programme, although depending on local labour costs, the mechanism of kit distribution and collection, and reduced sample stability in immunochemical testing, they might prove more practicable and affordable than immunochemical testing (Sect. 4.2.4, 4.3 and 4.4.2) **(I - B).**[Rec 4.1]

Immunochemical faecal occult blood tests

Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests. They are analytically and clinically more sensitive and specific, their measurement can be automated and the user can adjust the concentration at which a positive result is reported. Immunochemical tests are currently the test of choice for population screening; however, individual device characteristics including, ease of use by the participant and laboratory, suitability for transport, sampling reproducibility and sample stability are all important when selecting the iFOBT most appropriate for an individual screening programme (Sect. 4.2.5, 4.3 and 4.4.2) **(II - A).**[Rec 4.2]

DNA and other related new markers

Only tests for blood in faeces have been demonstrated to have the necessary characteristics to be suitable for population screening. DNA and other related new markers are currently unsuitable for screening, either singly or as members of a panel of tests (Sect. 4.2.6) **(III - D).**[Rec 4.3]

4.3 Analytical characteristics and performance

4.3.1 Analytical sensitivity

Analytical sensitivity or limit of detection describes the lowest concentration that an analytical system can detect with confidence. The detection system used by iFOBTs makes the test inherently more sensitive than guaiac-based systems. The concentration units quoted for analytical sensitivity depend on the method used for determination, for example mL of blood/g or mL of faeces, or mg (or µg) of haemoglobin/g or mL of faeces. Most manufacturers and scientific papers quote mg Hb/g faeces. The haemoglobin content should be determined with knowledge of the haemoglobin concentration in the blood used, and faeces should be measured as the wet weight of a formed stool sample. Some manufactures and studies also quote the concentration of haemoglobin not in faeces but in the buffer solution used for analysis, and this is different for different devices, making simple comparison of device sensitivity difficult e.g. the Hem-SP devices carry 0.3 mg faeces/mL buffer and OC-Sensor 10 mg faeces/mL buffer.

Given the variable consistency of faecal samples and the dependence upon diet and intestinal transit time, the relationship between patient samples and test samples prepared in the laboratory is often a poor one. Manufacturers may quote sensitivity on blood solutions rather than spiked faecal samples and if quoted for faecal samples, the time period between in-vitro addition of blood to faeces and analysis is unlikely to be typical of that between participant sampling and analysis in a screening programme. The unstable nature of samples used in FOBTs is discussed later in this chapter.

4.3.1.1 Analytical sensitivity and cut-off limits

Until recently it has not been possible to adjust the analytical sensitivity of FOBTs and so adjust the proportion of positive tests. This facility to adjust sensitivity is still not available for gFOBTs, with the exception of the simple process of hydrating the specimen prior to testing. With Hemoccult SENSA this process increases test sensitivity but at the expense of specificity, thereby increasing the false positive rate (Mandel et al. 1993; Ransohoff & Sandler 2002).

Point-of-care iFOBTs typically use an immunochromatographic technique that produces a coloured line where the antibodies and haemoglobin are immobilised. The presence of the line is detected by eye, and the limit of detection is dependent upon the configuration of the device, the characteristics of the antibodies and chromogens and the visual acuity of the reader. These iFOBT devices are suitable for small-volume point-of-care testing but are unsuitable for population screening and do not provide numeric results.

The heterogeneous nature of faeces and the inherent inconsistency in sample collection makes reliable quantitative measurement of blood in faeces impracticable. However, many of the automated immunochemical test devices that are suitable for population screening provide a numeric analytical result for the sample presented for analysis. These systems determine the turbidity or colour density of a reaction between haemoglobin and the antibody/chromogen system. Measurement is usually performed in a cuvette containing an aliquot of sample in buffer and added reagents (OC-Sensor, FOB Gold).

Whilst the results provided by these systems must not be considered quantitative measures of faecal haemoglobin, the numeric results provide an opportunity to select a cut-off limit above which a test can be defined as positive. This feature enables the user to adjust the positivity rate and thereby the clinical sensitivity and specificity of the test. Such a system enables colonoscopy referral rates to meet

the available colonoscopy resource. The clinical implications of manipulating the cut-off limit and/or the number of samples used for analysis is described later in this chapter.

Table 4.1 gives the analytical sensitivities quoted by manufacturers for a range of FOBT devices. Differences in quoted analytical sensitivity may reflect the use of different methods of assessment as well as product characteristics.

Table 4.1: Analytical sensicivities

Product name	Manufacturer/Supplier	Analytical Sensitivity
Guaiac-based test		
Coloscreen	Helena Laboratories, Texas, USA	0.9 mg Hb/g
Hema-screen	Immunostics Inc. 3505 Sunset Avenue, Ocean, New Jersey, 07712, USA	0.6 mg Hb/g
Hemoccult	Beckman Coulter Inc. Fullerton, CA 92835, USA	30% positivity at 0.3 mg Hb/g
Hemoccult SENSA	Beckman Coulter Inc. Fullerton, CA 92835, USA	75% positivity at 0.3 mg Hb/g
MonoHaem	Chemicon Europe Ltd	1.05 mg Hb/g
Hema-Check	Siemens PLC	6 mg Hb/g
HemaWipe	Medtek Diagnostics LLC, supplier; BioGnosis Ltd	2 mg Hb/g
Automated Immunochemical Test/*Analyser*		
OC-Sensor/OC-Sensor Diana & OC-Sensor Micro	Eiken Chemical Co., Tokyo, Japan	40 µg Hb/g
Hem-SP/MagStream HT	Fujirebio Inc. Japan	10 ng Hb/mL
FOB Gold/SENTiFOB analyser	Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy	14 ng Hb/mL

4.3.2 Analytical specificity and interference

In the context of gFOBT and iFOBT, *analytical* specificity is the ability of the test to detect human blood accurately without interference from other endogenous or exogenous components of the faeces. It does not include interference from blood produced from pathological or physiological sources, which is termed *biological* interference since the interference is not as a result of a weakness in the analytical system.

4.3.2.1 Analytical interference

gFOBTs use a non-specific reaction for detecting blood and whilst cheap and simple to use, they are inherently susceptible to positive interference from oxidising agents and compounds with oxidase or

peroxidase properties. gFOBTs are also subject to negative interference from compounds with reducing properties such as vitamin C. In its 2007 guidance to industry, the US FDA Centre for Device and Radiological Health illustrated the range of dietary substances known to interfere with gFOBTs: broccoli, cantaloupe, cauliflower, horseradish, parsnip, red radish, turnip, iron and vitamin C supplements, and haemoglobin from beef, chicken, fish, horse, goat, pig, rabbit and sheep.

Evidence suggests that although the gFOBT test is open to interference from normal diets, this is not substantial and is reported to be negated by a time delay of at least 48 h between sample collection and analysis (Sinatra, St John & Young 1999). A diet including 750 g of raw peroxidase rich fruit and vegetables daily is reported to cause false positive results however 750 g is an unusually large daily consumption. A systematic review of the effect of diet on gFOBT showed that dietary restriction was not necessary (Pignone et al. 2001). The five randomised trials included in the review all used gFOBT Hemoccult tests. None of the studies showed a statistically significant difference between the group in which peroxidise-containing food (red meat, no red meat, poultry, fish, or certain raw vegetables and fruits), nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), and vitamin C were prohibited compared with a control group without dietary restrictions (meta-analysis: absolute difference in positivity rate 0%; 95% CI, –1% to 1%). A cohort study conducted in Israel by Rozen, Knaani & Samuel (1999) on 944 asymptomatic subjects attending colorectal cancer screening (mean age 60.2±11.1) reported an overall gFOBT positive rate of 7.5%, while neoplasia was found in 16 (22.5%) subjects with positive gFOBT. Among subjects with and without dietary restriction, the positivity rates were 7.2% and 5.5% respectively (p = 0.26). These positivity rates are markedly higher than those observed in the UK screening pilots (1.6% in England and 2.1% in Scotland with an average of 1.9%) and are now observed in the fully rolled-out screening programme which does not advocate dietary restriction (UK Colorectal Cancer Screening Pilot Group 2004).

iFOBT brings a significant improvement in analytical specificity. The use of a specific antibody against human globin makes cross reactivity with dietary haemoglobin very unlikely, and the method used for detecting the antibody reaction can also be made largely free from interference from other dietary interference. Studies have not been published that demonstrate whether the reagents used in iFOBTs will detect haemoglobin variants. Polyclonal assays are unlikely to show cross-reactivity problems, but manufacturers should provide evidence that their analytical systems react similarly with all known haemoglobin variants. A recent evaluation has shown that with HbA1c, HbS, HbC, HbD, HbE and HbF using the Hem-SP/MagStream HT, OC-Sensor/Diana and FOB Gold Sentinal Systems, only HbF showed poor recovery and might give false negative negative results (Lamph et al. 2009).

Instant-View is an iFOBT that was used by the Australian health service, and since it requires sampling from the toilet bowl it is subject to other potential analytical interferences. In their US FDA 510(k) submission, the US supplier of Instant-View, Alfa Scientific Designs, disclosed decreased analytical sensitivity in the presence of toilet bowl deodorizers, fresheners and cleaner, and required that toilet bowl deodorizers/fresheners or cleaners be removed from the toilet bowl prior to collecting samples and that the toilet be freshly flushed.

Table 4.2 lists known gFOBT interferences. A good account is included in the MHRA Report of 2000 and summarized by Starkey (2002).

4.3.2.2 Biological interference

Any physiological process or non-colorectal cancer related pathological lesion that increases the loss of blood into the intestine is a source of biological interference. Although aspirin and NSAIDs pose potential interference, studies have shown either no effect or an increased sensitivity to the detection of cancer and adenomas among those who are taking aspirin.

Table 4.2: gFOBT Analytical interference

Positive interference	Comment	Reference
Non-human blood (beef, pork, chicken, pheasant, salmon, sardines, black pudding, German blutwurst, French boudin noir, Spanish morcilla and liver)	Reduced by cooking. Avoid red meat for 3 days prior to sampling. Meta-analysis suggests dietary restriction not necessary	(Illingworth 1965; Fludger et al. 2002)
Myoglobin		(Lifton & Kreiser 1982; Achord 1983; Welch & Young 1983; Scriven & Tapley 1989; Anderson, Yuellig & Krone Jr. 1990)
Iron	Mixed reports about whether iron supplements interfere	
Providone-iodine antiseptic	Use on perianal area or in urinary catheters should be avoided since iodine will oxidise guaiaconic acid.	(Said 1979)
Contact with toilet sanitizers in toilet water	Potential for negative and positive interference. gFOBT less than iFOBT. Reported in chlorine-releasing agents	(Imafuku, Nagai & Yoshida 1996)
Raw fruits & turnips, broccoli, horseradish, cauliflower, cantaloupe, parsnip and red radish	Large daily consumption only, causes interference. Caused by peroxidases that act like haemoglobin and give false positives. Cooking for 20 mins at 100°C destroys peroxidases and a delay of 2 days between collection and analysis is also effective as long as a non-hydrated gFOBT is used	(Illingworth 1965; Sinatra, St John & Young 1999)
Negative interference	Comment	Reference
Vitamin C (Ascorbic acid)	Reducing agents counters oxidising effect on guaiaconic acid. Vitamin C intake should be <250 m/d. Normal diet unlikely to interfere but high dose supplements might do so	(Jaffe et al. 1975; Garrick, Close & McMurray 1977; Jaffe & Zierdt 1979)
Degradation of haem	Haem degrades slowly a process that is accelerated if the faecal sample remains moist and warm	CEP Report 2006 (Bennitt, Burtonwood & Halloran 2006)
Contact with toilet sanitizers in toilet water	Potential for negative and positive interference. gFOBT less than iFOBT	(Imafuku, Nagai & Yoshida 1996)

Aspirin and NSAIDs

One double-blind RCT and one cohort study investigated whether the use of regular aspirin or NSAIDs is a risk factor for a false-positive FOBT result. A double-blind RCT (Greenberg, Cello & Rockey 1999) was conducted on healthy volunteers aged 29.8 ± 0.6 years who were randomised to placebo and those receiving doses of 30 mg, 81 mg, and 325 mg of aspirin. Short-term (30 days) use of low-dose aspirin did not induce sufficient intestinal injury to cause positive FOBTs (number of GI erosions aspirin group: 6/30 (20%); placebo: 1/10 (10%) p = 0.66). A cohort study (Kahi & Imperiale 2004) showed no difference in the prevalence of colonoscopic findings that would potentially explain a positive FOBT result between regular aspirin or NSAID users and non-users, even after adjusting for factors that affect the risk of a lesion that would account for a positive result (absolute difference 2% (95% CI -10–14), p=0.7). The study also found no relationship between the dose of aspirin and the likelihood of colonoscopic findings (chi-squared test for trend p=0.6). Overall, advice to patients to

restrict their diet and avoid NSAIDs and vitamin C does not appear to change positivity rates. This finding was consistent across all studies, regardless of the intensity of the restriction. A recent report by Levi et al. (2009) showed an increase in sensitivity but no loss of specificity of iFOBT (OC-Sensor) for detection of cancer and advanced adenomas in those using asprin/NSAIDs or anticoagulants.

Anticoagulants

Anticoagulants present a further source of biological interference. The effect of anticoagulants on the false-positive rate in a population-based FOBT screening programme was evaluated in two studies (Bini, Rajapaksa & Weinshel 2005; Clarke et al. 2006). The cohort study conducted within the Scottish arm of the national colorectal cancer screening pilot on 846 subjects aged 50–69 years old showed that taking anticoagulant medication (aspirin, COX-2 inhibitors, other NSAIDs and warfarin) at the time of testing is associated with a statistically significant 6.4% increased rate of negative colonoscopy. Diagnosis of colorectal neoplasia was higher in the no-anticoagulant group compared with the anticoagulant medication cohort (56.5% vs. 47.5%; absolute difference 9%, p=0.012). A study in an American healthcare system programme looked at all patients taking warfarin who were referred for the evaluation of a positive FOBT (Bini, Rajapaksa & Weinshel 2005). For each patient taking warfarin, an age- and gender-matched control was enrolled. The positive predictive value of FOBT for gastro-intestinal lesions consistent with occult blood loss in patients taking warfarin was similar to that in the age- and gender-matched control group of subjects with a positive FOBT who were not taking oral anticoagulants (59.0%, 95% CI, 52.3–65.8%; 53.8%, 95% CI, 47.0–60.6%; p=0.27).

Table 4.3 summarises sources and mechanisms of biological interference which will reduce the specificity of either gFOBT or iFOBT analysis.

Table 4.3: Biological interferences

Physiological	Comment	Reference
Loss from the gums after vigorous teeth brushing		
Menstrual bleeding	-	-
Pathological		
Inflammatory bowel disease (Crohns disease, colitis)		(Rockey et al. 1998)
Gastritis from alcohol or chemotherapeutic drugs	-	
Gastric Cancer		(Zhou, Yu & Zheng 1999; Zappa et al. 2007)
Anti-inflammatory drugs (ibuprofen, naproxen, corticosteroids, phenybutazone)	Increased blood loss of 1-2 mL/d. 5% of those on high dose NSAIDs lost 5mL/d	(Moore, Derry & McQuay 2008) (Levi et al. 2009)
Aspirin	No iFOBT interference reported in low dose aspirin. High-dose blood loss 5 mL/d	(Ahlquist et al. 1985), (Moore, Derry & McQuay 2008) (Levi et al. 2009)
Proximal intestinal tract inflammation (gastritis, oesophagitis and gastric and duodenal ulceration)		(Rockey et al. 1998)
Anticoagulation therapy	2005 study showed no effect from warfarin	(Bini, Rajapaksa & Weinshel 2005)
Perianal bleeding	-	-

4.3.2.3 Dietary and drug restrictions

Potential interference of diet and drug intake on test performance has been pointed out above (Sect. 4.3.2.1 and 4.3.2.2) and the organisational aspects of drug and dietary restriction are discussed in Ch. 2 (Section 2.5.1.2). Whilst most gFOBT manufacturers recommend dietary advice, the potential

detrimental impact on participation rates makes it unattractive. One study used an immunochemical test and compared the participation rates of two groups, one with and one without dietary restriction (Cole & Young 2001). Two further studies (Cole et al. 2003; Federici et al. 2005) compared participation rate in a guaiac test with dietary restriction and in an immunochemical test without dietary restriction. Predictably, all three studies found greater participation when the diet was unrestricted. However, these studies and their data are not sufficient to exclude the possibility of other factors contributing to the outcomes.

4.3.3 Other factors influencing analytical performance

4.3.3.1 Prozone effect

Immunochemical analysis is prone to giving falsely low results when the analyte being tested is at markedly elevated concentrations. This well described interference is called the prozone or "hook" effect. The concentration of haemoglobin at which an iFOBT exhibits this effect needs to be very high and should be disclosed by the manufacturer. If an analytical method exhibits a prozone effect, then the measurement system should be able to detect erroneous results and warn the analyst. This is a requirement of U.S. FDA 510(k) submissions.

4.3.3.2 Sample quality

The quality of the sample is very important; it must be reproducible and representative of the stool, to be of the required volume and be adequately preserved. Many of the issues that impinge on sample quality have been discussed earlier. The stability of haemoglobin in faeces is an important consideration when selecting the preferred test, developing arrangements for sample transport to the laboratory and determining the urgency of analysis on the arrival of samples in the laboratory.

The haem moiety used in gFOBTs is more stable than the globin moiety used in iFOBTs. Transport of a dried sample, which is used for most guaiac test kits, provides greater stability than that in wet buffer which is usually used for immunochemical tests. The acceptable time period between sampling and testing is defined by the product manufacturers in their Instructions For Use (IFU). For gFOBTs the maximum time period is usually between 14 and 21 days; for iFOBT it is much less.

Haem in haemoglobin is degraded slowly after collection; if samples are collected onto filter paper, the design of the test device and envelope should maximise the speed of drying and so help preserve the sample. Young et al. demonstrated the deterioration of wet samples in a study using gFOBT in 1996 (Young, Sinatra & St John 1996). The UK NHS MHRA report of 2000 illustrated the influence of excessive sample loading, high temperature storage, and exposure to sunlight on 12 occult blood kits (Pearson, Bennitt & Halloran 2000). The UK NHS CEP report of 2006 reported the effect of sample storage time upon positivity for four gFOBT kits, the change from positive to negative test result being most marked with those test kits that have the lowest limit of detection (Bennitt, Burtonwood & Halloran 2006). For gFOBT, a regression study by Faure et al. investigated the influence of temperature and moisture on gFOBT sensitivity. In this study it was observed that the positivity rate of Hemoccult II in a 10-year screening programme showed a significant change between 1.61% in summer to 2.80% during the winter (Faure et al. 2003). No significant effect of temperature alone was observed: the positive rate decreased from 74.0% at 4°C in the presence of silica gel to 68.0% at 30°C in the presence of water (p=0.52). In this study the decrease in positive rate due to the presence of moisture was statistically significant (84.0% at 4°C and 100% humidity, 58.0% at 25°C with silica gel; p=0.007).

Globin in haemoglobin is an easily degraded protein moiety and more susceptible to denaturation than haem. Proteolysis of globin should be minimised between sample collection and analysis. Whilst appropriate constituents in collection buffer solutions might reduce degradation, the stability of globin in the wet collection systems used by most iFOBTs is poor compared with haem used in gFOBTs. The concentration of haemoglobin in the buffer solutions after sampling can be very low, typically 20ng/mL with the collection device used by the MagStream HT. At these low concentrations the haemoglobin molecule is susceptible to decomposition and may be adsorbed onto the surface of the collection vessel and measurement cuvette. Buffers that are rich in proteins such as bovine serum albumin (BSA) and haptoglobin can minimise adsorption and help stabilise the haemoglobin. Unpublished data from the manufacturers of the immunochemical devices Hem-SP and OC-Sensor show good stability at refrigerator temperatures (4°C) but marked deterioration with rising temperature. Vilkin et al. (2005) and Rozen et al. (2006) showed, over 21 days, no significant change at 4°C or 20°C but a daily fall of 3.7% ± 1.8 at 28°C with the iFOBT OC-Micro system (*Eiken Chemical Co., Tokyo, Japan*). Rozen used storage in a refrigerator and supplied an opaque double zip-lock bag for such storage. Fraser et al. (2007) reported the successful use of dried samples for iFOBTs using two Immunostics products (*Immunostics Inc. Sunset Avenue, Ocean, New Jersey, USA*). Hema-screen Devel-A-Tab was used to collect the sample and Hema-screen Specific as the immunochemical assay system. The low concentrations of haemoglobin detectable in iFOBT devices increases susceptibility to stability problems. Whilst sample stability has not presented a major difficulty for programmes using gFOBTs, it is likely to do so for those adopting wet sample collection with iFOBTs. The acceptable time between collection and analysis is markedly influenced by ambient temperature during storage and transport, and this will depend on transport and weather conditions.

Between December 2008 and May 2009, the Australian Screening Programme encountered stability problems with the Haem-ST/MagStream HT system (Australian Government 2009). Positivity levels fell markedly during the 6-month period, and participants will require retesting. Very high summer temperatures and the introduction of a new buffer with a lower protein concentration may have contributed to haemoglobin instability in this programme and a consequent reduction in positivity rates. A recent report describes retrospective analysis of measured haemoglobin over several years by the screening programme in Northern Italy (Grazzini et al. 2010). The study reveals significant seasonal variation in the positivity rates of in the OC-Sensor iFOBT that may be attributed to by high summer temperatures. Manufacturers of iFOBT devices specify stringent storage and transit conditions to minimise the sample deterioration. These conditions present a practical challenge to the organisation of iFOBT-based screening programmes.

4.3.3.3 Device consistency

The ability of iFOBT and gFOBT kits to maintain consistent performance across reagent batch changes and product redesigns is important for population screening since minor changes in product sensitivity and specificity can greatly change the number of patients referred to colonoscopy. Companies need to be able to demonstrate good quality manufacturing practice and quality assurance procedures that minimise batch-to-batch variation. Guaiac gum is a natural product and is therefore more susceptible to product inconsistency than manufactured monoclonal antibody reagents that can be used by iFOBTs. Polyclonal antibodies, which are used for each of the current automated iFOBTs, are susceptible to batch-to-batch variation, and therefore an understanding of the batch size of all reagent components is important. In a market with many small manufacturers, the long-term viability of the product and company should also be considered.

4.3.3.4 Analytical quality assurance – Internal Quality Control (IQC) and External Quality Assessment Schemes (EQAS)

Rigorous analytical quality assurance procedures must be adopted by laboratories providing gFOBT and iFOBT analysis for population screening. To minimise analytical and procedural variability, the

number of laboratories used for population screening should be small. In the English programme, laboratories typically serve a population of 10–15 million, approximately 10–16 % of which will be within the screening age group. All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007, *Medical laboratories - Particular requirements for quality and competence* (http://www.iso.org/iso/iso_catalogue.htm) The laboratory should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and in clinical quality assurance procedures. The laboratory staff should be appropriately trained and competent in the use of the analytical device/ instrumentation, quality control and assessment procedures and associated information technology.

For those laboratories using visually read gFOBTs, the design of the test kit will influence the reliability of analysis. Reproducibility in detecting the blue gFOBT colour in the presence of dark faecal pigments depends on good staff training and experience but can be improved by other factors. The visual acuity and colour perception of the reader should be professionally checked and monitored. The colour of the test card surrounding the sample, the colour of surrounding walls and the colour temperature and brightness of artificial lighting all should be considered. The opportunity for errors due to operator fatigue should be minimised by enforcing periodic work breaks. The competence of staff to perform visual tests should be checked before they commence each batch of analysis, typically using pre-loaded test kits with known positivity that is hidden from the operator. A rigorous monitoring system should be adopted to identify staff who have spot positivity rates which are markedly different to the mean or who exhibit marked variability.

Most gFOBTs and point-of-care iFOBT devices have a means of checking the integrity of the device and reagents by way of a quality control check integral to the device. For gFOBT, this control can check whether guaiac has been applied across the whole of the test area and whether the hydrogen peroxide reagents are working correctly. Point-of-care iFOBT devices provide a similar check of reagent integrity but are unsuitable for population screening.

The case for automation in population screening programmes is a strong one, and should significantly influence the choice of an acceptable occult blood testing system. Automated iFOBT analysis will require internal quality control procedures appropriate to the chosen technique and instrument. As a minimum, laboratories should adopt the manufacturers' instructions for use, and give consideration to what additional internal quality control measures can be used to check instrument accuracy and imprecision throughout the period of analysis. Good analytical performance is particularly important at the selected cut-off concentration, and quality control measures should reflect that requirement.

Participation in an external quality assessment scheme (EQAS) is seen as mandatory for tests performed in a clinical laboratory. Participation in an EQAS enables assessment of bias between participating laboratories, and is particularly important for a national screening programme utilising several laboratories. The availability of an EU-wide EQAS is desirable. National population screening programmes should have quality assurance procedures that enable oversight of the analytical performance of all screening laboratories. Satisfactory performance in an EQAS provides an objective criterion of competence.

A summary of the three iFOBT systems that have some of the characteristics suitable for population screening is provided in Table 4.4.

Table 4.4: Comparative table of automated iFOBT

Hem-SP/MagStream HT

Alternative name(s): Developed from Immudia-Hem-SP (Marketed as HaemSelect in the US)

Manufactured by: Fujirebio Inc. Japan

Sold by: Fujirebio Europe B.V. (http://www.fujirebio.co.jp/english/index.html)

Principle of measurement system: MagStream Hem-Sp® is based on magnetic particle agglutination. The faecal specimens are incubated with magnetic gelatine particles which are ferrite and gum Arabic coated with rabbit anti-human haemoglobin antibodies. The solid particles are collected in the centre of microplate wells by magnetic attraction and inclined to about 60 degrees and examined for change in particle aggregates. In the presence of human haemoglobin, the particles remain aggregated in a spot with minimal change (positive result). In the absence of human haemoglobin, particles flow down the slope (negative result). The appearance of particle aggregates is interpreted by MagStream HT using CCD image capture and computer determination of the length of the line of magnetic particles. The company recommends that 1 of 2 samples need to be positive and state that the measurement system has not been designed for quantitative measurement. This system has been developed to give a sharp cut-off at a concentration of 20 ng/mL and not to provide quantitative measurements for user-defined cut-off concentrations, and is not CE marked for this purpose.

Recommended number of separate samples used for assessment: 2 samples

Method of sample collection: Stick in buffer held within the device

Means of reading: MagStream HT, an automated instrument which holds 400 samples and has a memory capacity of 2 million test results

Speed of analysis: 960 tests per hour (MagStream HT)

Quantity collected by sampling device: 0.3 mg of faeces

Volume of buffer in collection device: 1 mL

Analyser sample volume: 25 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: It is being used in both France and Slovenia.

Cut-off level: Not designed or CE marked for an adjustable cut-off

Limit of detection: 10 ng/mL

Use in population screening: Japan, France and Slovenia

Recent pertinent scientific papers: (Launoy et al. 2005; Morikawa et al. 2005; Morikawa et al. 2007)

Website URL: Fujirebio

Fujirebio Inc Japan

http://www.fujirebio.co.jp/english/product/immunological.html

OC-Sensor

Alternative name(s): OC-Hemodia, OC light (not available in EU)

Manufactured by: Eiken Chemical Co., Tokyo, Japan

Sold by: Mast (UK), Alfa Wassermann (Italy), Pharmatrade (Israel)

Principle of system: Latex agglutination using polystyrene latex particles coated with polyclonal anti haemoglobin Ao antibodies. The assay uses a 6-point standard curve, and measurement is made at 600 nm with an algorithm which uses a kinetic endpoint.

Recommended number of separate samples used for assessment: 1 sample

Method of sample collection: Serrated stick in buffer held within the device

Means of reading: OC-Sensor Diana & OC-Sensor Micro (successor to OC-Sensor Neo) are both automated instruments and are both CE marked. The Diana has a memory capacity for 100 000 test results

Speed of analysis: 280 samples per hour (OC-Sensor Diana)

Quantity collected by sampling device: 10 mg of faeces

Volume of buffer in collection device: 2 mL

Analyser sample volume: 35 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: Reported to have been agreed by the UK post office

Cut-off level: CE marked for a user defined cut-off. Default setting 100 ng/mL

Limit of detection: 20 ng/mL in buffer

Use in population screening: The Netherlands (van Rossum et al. 2008; van Rossum et al. 2009), Northern Italy (Castiglione et al. 2000), US, Uruguay (Fenocchi et al. 2006) and France

Website URL: http://www.eiken.co.jp/en/company/index.html

URL: http://www.eiken.co.jp/en/product/index.html#anc03

FOB Gold

Manufactured by: Sentinel Diagnostics SpA, Milan, Italy

Principle of system: The FOB Gold reagents use an antigen-antibody agglutination reaction between human haemoglobin and polyclonal anti-human haemoglobin antibodies coated on polystyrene particles. Agglutination is measured as an increase in absorbance at 570 nm and is proportional to the concentration of human haemoglobin contained in the sample. The calibrator is a lyophilized material containing human haemoglobin, and this is used to generate a six-point calibration curve using serial dilutions of the reconstituted material. The manufacturer provides lyophilized quality control preparations at two haemoglobin concentrations. The total reading time is 8 minutes.

Means of reading: The FOB Gold reagents can be used on any suitable immunoassay automated analyser although the manufacturer provides the SENTiFOB analyser

Speed of analysis: 75 tests/hr (SentiFOB)

Quantity collected by sampling device: 10 mg of faeces

Volume of buffer in collection device: 1.7 mL

Analyser sample volume: 10 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: Not known

Cut-off level: CE Marked for a user defined cut-off

Limit of detection: 14 ng/mL buffer

Range Measuring range: 15-1000 ng/mL.

Use in population screening: Italy (Rubeca et al. 2006) & France

Recent pertinent scientific papers: (Fraser et al. 2008)

Website URL: http://www.sentinel.it/uk/

4.3.4   Recommendations

Sample stability between collection and analysis

Whilst a maximum period of 14 days between collection and analysis is frequently quoted for many guaiac faecal occult blood tests, that quoted for immunochemical tests is significantly shorter. Until more stability data are published, screening programmes should adopt the conditions and period of storage described in manufacturer's Instructions for Use having determined that they are appropriate for local conditions which might expose samples to high temperatures for long periods of time (Sect. 4.3.3.2) **(III - A).**[Rec 4.4]

Test interference - drug and diet restriction

Dietary constituents present potential interference in guaiac faecal occult blood tests. Dietary restricttion has not been demonstrated to significantly increase screening specificity, and risks reducing participation rate. The potential for dietary interference is significantly less for immunochemical tests. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported dietary restriction is not indicated for programmes using either guaiac-based or immuno-chemical tests (Sect. 4.3.2.1, 4.3.2.3) **(II - D).**[Rec 4.7]

Interference from bleeding associated with drugs such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants (e.g. warfarin) present potential interference in both guaiac and immuno-chemical faecal occult blood tests. Although the literature carries some contradicting reports of the effect of anticoagulants on screening outcome, drug restriction is not recommended for population screening programmes using either guaiac-based or immunochemical tests (Sect. 4.3.2.2, 4.3.2.3) **(III - D).**[Rec 4.8]

Faecal sampling/collection system

Many factors influence the uptake and reliability of sample collection. Inappropriate implementation can result in grossly misleading results. No single collection methodology is supported by the literature; however, the following factors should be considered when selecting a device for taking samples in population screening:

- The distribution process should be reliable and reach all selected subjects.

- The laboratory should be able to unambiguously identify the subject ID on the test device perhaps using a suitable barcode.

- The laboratory should be able to check the manufacturer's device expiry date on each returned device.

- The instructions for using the device must be simple and clear.

- The device should to be simple and easy to use by the target population.

- The device should leave minimal opportunity for collection error.

- The device should facilitate consistency in the volume of sample collected.

- The device/instructions should discourage inappropriate repeat sampling into/onto the sample device.

- Misuse of the device by participants should not cause loss of sample buffer.

- The system should not be susceptible to interference from toilet bowl disinfectants, etc.

- The screening participant should be able to record the date of sample collection to ensure the laboratory can verify receipt within an acceptable sample stability period.

- The process used by the subject for returning the device should be simple, reliable, safe and, when appropriate, should meet EU postal regulations.

A local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable (Sect. 4.2.3, 4.2.4, 4.3.2.1, 4.3.3.4) **(VI - A).**[Rec 4.9]

Laboratory organisation:

- **Number of laboratory sites**

  Population screening necessitates the receipt, measurement and recording of thousands of tests each day. The samples should be analysed without delay to avoid further sample denaturation and avoid an increase in false negative results. Inter-laboratory analytical imprecision is well described and can be observed through established external quality assurance schemes. Improved consistency is achieved by adopting common analytical platforms, analytical and quality standards and shared staff training. The analysis needs to be reproducible across a screening population and therefore the number of analytical centres should be minimised with automated analytical systems utilised wherever possible and agreed common testing procedures adopted by each centre (Sect. 4.3.3.4) **(VI - B).**[Rec 4.10]

- **Laboratory staff**

  All laboratories providing population screening should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and with clinical quality assurance procedures (Sect. 4.3.3.4) **(VI - B).**[Rec 4.11]

- **Laboratory accreditation and quality monitoring**

  All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 *Medical laboratories - Particular requirements for quality and competence*. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS, Sect. 4.3.3.4) **(VI - B).**[Rec 4.12]

- **Distribution of FOBT kits by mail**

  Distribution and receipt of FOBT kits using local postal services can be an effective means of reaching the designated population (Ch. 2, Rec. 2.15, Sect. 2.5.1.1 and Sect. 4.4.3.4) **(I - B).**[Rec 4.13]

Identification of participants and test results

Automated check protocols should be implemented to ensure correct identification of the screened population and complete and accurate recording of individual screening participation and test results (see Ch. 2, Rec. 2.18, Sect 2.5.1.3) **(VI - A).**[Rec 4.15]

Classification of test results

Protocols should be implemented to ensure standardised and reliable classification of the test results (Ch. 2, Rec 2.19, Sect. 2.5.1.3) **(VI - A).**[Rec 4.16]

Quality Assurance

- **Quality assurance of gFOBT testing**

  Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures. To minimise variability and error associated with visual test reading, including manual results input, the following procedures should be considered (Sect. 4.3.3.4) **(VI - B):**[Rec 4.17]

o Use of appropriate temperature for artificial lighting and neutral-coloured walls in the reading laboratory;

o Use of a national laboratory training programme to prosper consistency of interpretation;

o A blinded internal QC check each day for each analyst prior to commencing testing;

o Adoption of a monitoring programme to identify operator related analytical performance (e.g. positivity variability and bias); and

o Double entry of test results

- **Quality assurance of iFOBT testing**

Consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures (Sect. 4.3.3.4) **(VI - B).**[Rec 4.18]

- **External quality assessment**

A European external quality assessment scheme should be developed to facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening (Sect. 4.3.3.4) **(III - B).**[Rec 4.19]

- **Outcome monitoring**

All aspects of laboratory performance in respect of the screening test should be part of a rigorous quality assurance system. Uptake, undelivered mail, time from collection to analysis, analytical performance (internal QC and external QA), positivity rates, lost & spoilt kits and technical failure rate, technician performance variability and bias should each be subject to rigorous monitoring (Sect. 4.3.3.4) **(VI - A).**[Rec 4.20]

- **Quality of information**

The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (see Ch. 3, Rec. 3.9, Sect. 3.3.2) **(III - A).**[Rec 4.21]

4.4   Clinical performance

4.4.1   Description of terms used to describe test effectiveness

gFOBT screening has been proven to be effective in reducing colorectal cancer mortality (Hewitson et al. 2007). In randomised trials the reduction in cause-specific mortality ranged from 15% (Hardcastle et al. 1996) to 33% (Mandel et al. 1993). Such a large variance in mortality can be explained by test differences, different numbers of faecal samples, different intervals between invitation cycles (one-

year or two-year) and different responses to invitation associated with the characteristics and composition of the population screened. The sensitivity and specificity quoted for a test will therefore be influenced both by the test's analytical characteristics and the context in which the test is used and evaluated.

gFOBTs come in two forms, the conventional form with normal sensitivity and the more sensitive variety, Hemoccult SENSA, in which the sample is hydrated before analysis. Hemoccult SENSA performs quite differently from the gFOBTs used in European trials (Hardcastle et al. 1996; Kronborg et al. 1996) and is both more sensitive and less specific. Comparison of the clinical performance of gFOBT and iFOBT is complex because iFOBTs can have different levels of specificity and sensitivity indeed they may have variable positive cut-off concentrations. Changes in cut-off concentrations result in different clinical performance characteristics.

Although only one population-based RCT has been described with iFOBT (van Rossum et al. 2008), the many published diagnostic accuracy studies provide information on the comparative ability of current tests to distinguish subjects with or without colorectal cancer and adenoma and can be considered an acceptable indication of the satisfactory performance of iFOBT in population screening (Burch et al. 2007).

Diagnostic accuracy studies have compared:

a) subjects performing one or both tests (gFOBT and iFOBT) and performing a total colonoscopy (or sigmoidoscopy) independently from the result of the test (cohort studies);

b) subjects performing one or both tests and undergoing colonoscopy if one or both tests are positive (cohort studies);

c) Diagnosis determined beforehand and the test performed subsequently (case-control studies); and

d) Different subjects performing different tests.

Colorectal cancer, large adenomas ($\geq$ 10 mm), high-risk adenomas (high-grade dysplasia, villous change, serrated histology or $\geq$ 3 polyps), all adenomas (including small adenomas), alone or combined have been used as reference standards in the various studies.

The comparative clinical performance of the different tests has usually been based on the following indicators: Sensitivity, specificity, Positive Predictive Value (PPV), false positive rate, likelihood ratio for a positive or a negative test which is derived from sensitivity and specificity (sensitivity/(1-specificity)) for + LR; (1-sensitivity)/specificity for –LR.

All of these parameters derive from the well-described 2*2 table

		Disease Present	Disease Absent	
		+	-	Total
Positive Test	+	a	b	a+b
Negative Test	-	c	d	c+d
	Total	a+c	b+d	

Where, *a* are true positive, *b* are false positive, *c* are false negative and *d* are true negative

Sensitivity = a/(a+c)
Specificity = d/(b+d)
PPV = a/(a+b)

"True" in true positive, is an abstract concept because in practice a reference standard must be adopted. For colorectal cancer screening, true is usually defined by the outcome of total colonoscopy, the best practical diagnostic procedure we have though it does not have a sensitivity of 100%. In a clinical setting it is not always possible to perform a total colonoscopy on all subjects who have negative screening tests, so it is difficult to estimate the number of false negatives (c) and true negatives (d). The difficulty of estimating false negative has a great impact on sensitivity but much less so on specificity. In fact (c) is a number much lower than (d), so that the sum c+d (i.e. the number of negatives to the test) is a small overestimate of d.

For sensitivity, (c) is a significant proportion of (a+c), so that it is necessary to have a direct estimate of the number of false negatives. Very often this estimate is obtained by measurement of the interval cancers (i.e. the number of colorectal cancers that are diagnosed in subjects negative to the test during defined interval of time). Clearly the reliability of the estimated number of false negatives will depend on the time interval, and that will increase as time elapses. It is therefore important when comparing estimates of sensitivity obtained in this way to verify that the time interval used is the same.

The ideal theoretical approach to estimating cancer-screening performance would be to obtain the disease status using a "gold-standard" method that is independent of the screening method. For colorectal cancer, the disease status is usually determined from a histological examination of biopsy specimens of those with positive test results, because it is not ethically acceptable to collect biopsies from all individuals undertaking a screening test. The sensitivity and specificity of screening test are therefore usually estimated using interval cancers. As initially described by Day (1985) interval cancers will not include slow-growing cancers missed by the test and not evident between two screening events (therefore clinical sensitivity will be overestimated). Conversely, interval cancers will include fast-growing cancers not present at the time of the screening test, but developing during the interval period (thus underestimating clinical sensitivity). This limitation is common to all screening procedure evaluations.

Programme sensitivity is an estimate of sensitivity (i.e. the number of CRC detected/the number of cancers detected plus the number of interval cancers occurring in a certain interval of time) and is biased toward overdiagnosis of CRC (i.e. it estimates diagnosis of CRC that would never occur clinically). For this reason it is sometime preferable to give an estimate of sensitivity based on the ratio between interval cancers (in a defined time period) and the number of cancers expected in the same period (more precisely, 1- (interval cancers occurred in x years/expected cancers in x years)). This estimate gives an idea of cancers anticipated by screening, and it is not affected by overdiagnosis.

It is also worth noting that from a practical point of view, the choice of the test (or combination of tests) is not based on clinical sensitivity and specificity but on the determination of detection rate (for cancer or adenomas) and its correlation with positivity being first correlated to sensitivity and latter to specificity.

4.4.2 Comparative clinical performance - gFOBT and iFOBT

Many studies comparing iFOBT and gFOBT have been performed in the last 8 years, and several systematic reviews of the literature have been undertaken more recently.

In 2007 Kerr published a systematic review by the Health Technology Assessment (NZHTA) of New Zealand which had the aim of identifying the international evidence for the clinical and cost effectiveness of screening tests for colorectal cancer (Kerr et al. 2007). This review included all primary research published as full original reports and secondary research, systematic reviews and meta-

analyses published since November 2004. It also included seven eligible primary research papers (Rozen, Knaani & Samuel 1997; Rozen, Knaani & Samuel 2000; Saito et al. 2000; Zappa et al. 2001; Cheng et al. 2002; Cole et al. 2003; Ko, Dominitz & Nguyen 2003) and five eligible secondary research papers; Australian Health Technology Advisory Committee (AHTAC) (1997), Conseil d'Évaluation des Technologies de la Santé du Quebec (2000), Canada, Craven UK (Craven 2001), Young World Health Organization and World Organization for Digestive Endoscopy (Young et al. 2002), Piper Blue Cross Blue Shield Association Technology Evaluation Center US (Piper 2004).

The review concluded that "there is limited definitive evidence regarding superior immunochemical FOBT performance over the guaiac tests. However, evidence from cross-sectional studies suggests that the immunochemical test HemeSelect, *Beckman Coulter Inc. Fullerton, CA, USA...* is comparable, or superior, to guaiac testing... The conclusions on this topic should be revisited if further reliable evidence on the comparative performance of screening FOBTs becomes available".

A similar conclusion was reached in a systematic review commissioned by the UK NHS and undertaken by the Centre for Reviews and Dissemination of the University of York in 2007 (Burch et al. 2007) which examined the literature until 2004. The review included 59 studies 39 evaluated gFOBTs, 35 evaluated iFOBTs and one evaluated sequential FOBTs. It concluded that there was no clear evidence from direct or indirect comparisons to suggest that guaiac or immunochemical FOBTs performed better. However amongst iFOBTs, Immudia-HemSP (now Hem-SP) appeared to be the most sensitive and specific.

In the four years since 2004, six studies comparing the performance of gFOBT and iFOBT have been published (Levi et al. 2006; Smith et al. 2006; Allison et al. 2007; Guittet et al. 2007; Dancourt et al. 2008; van Rossum et al. 2008). Some further studies have investigated the accuracy of iFOBTs which, although without a direct comparison with gFOBTs, confirmed the performance of iFOBTs which was reported in the following studies (Morikawa et al. 2005; Castiglione et al. 2007; Levi et al. 2007).

In Australia, Smith et al. (2006) performed a paired comparison of an iFOBT (InSure) with a sensitive gFOBT (Hemoccult SENSA); 2351 asymptomatic and 161 symptomatic subjects were requested to perform both FOBTs. iFOBT returned a true-positive result significantly more often in cancer (n = 24; 87.5% vs. 54.2%) and in significant adenomas (n = 61; 42.6% vs. 23.0%) while the false-positive rate for any neoplasia was marginally higher with the iFOBT than the gFOBT (3.4% vs. 2.5%; 95% CI of difference, 0–1.8%): the PPV for cancer and significant adenomas was slightly better for iFOBT (41.9% vs 40.4%).

In Israel, Levi et al. (2006) compared, a gFOBT with an iFOBT (OC-MICRO, now OC-Sensor) in a small number (151) of patients referred for colonoscopy either because of a positive gFOBT or because they were above average risk of colorectal cancer. Sensitivity, specificity, and positive predictive value for significant colorectal neoplasia were 75%, 34% and 12%, respectively, for gFOBT, and were 75%, 94% and 60% for iFOBT. For a positive gFOBT, 4 times more colonoscopies were needed to identify a significant neoplasm compared with iFOBT, and at more than 4 times greater cost.

In France, Guittet et al. (2007) compared the performance of gFOBT and iFOBT (Immudia-HemSP (now Hem-SP)) among 10 673 average-risk persons aged 50–74 years. Colonoscopy was offered only if either FOBT was positive. The threshold for a positive iFOBT was varied between 20 ng/mL and 75 ng/mL. Overall, the results depended on the adopted iFOBT threshold. At the lower threshold (20 ng/mL), iFOBT detected 1.5 times as many cancers and nearly 2.6 times as many high-risk adenomas as gFOBT; however, it also increased the relative false-positive rates (2.17 times more frequent for each relevant lesion detected in iFOBT as compared to gFOBT). It is worth noting that at a threshold of 75 ng/mL, iFOBT detected 90% more advanced neoplasms with a significant 33% decrease in the false-positive risk. A further publication from this study (Guittet et al. 2009a) reported that the gain in sensitivity from using iFOBT vis gFOBT was proportional to the degree of blood loss from the lesion and its location. The benefits for cancer detection were restricted to lesion of the rectum.

In the USA, Allison et al. (2007) prospectively compared two types of FOBTs, a sensitive gFOBT (Hemoccult SENSA) and a manual iFOBT (Flexsure). A large number of patients (7394 subjects were eligible for the study) were requested to perform both tests. All patients positive for either FOBTs were invited to have a total colonoscopy, whereas all patients negative to FOBT were advised to have a sigmoidoscopy. All cancers occurring during the two years following the test were identified, so that it was possible to estimate the absolute sensitivity and specificity for detecting advanced neoplasms in the left colon within two years after the FOBT screening for the two tests administered separately and in combination. The sensitivity for detecting cancer was 81.8% (95% CI = 47.8% to 96.8%) for the iFOBT and 64.3% (95% CI = 35.6% to 86.0%) for the gFOBT. The sensitivity for detecting distal advanced adenomas was higher for gFOBT than for iFOBT 41.3% (95% CI = 32.7% to 50.4%) vs 29.5% (95% CI = 21.4% to 38.9%). PPV was much higher for iFOBT than for gFOBT for distal cancer (5.2% and 1.5% for iFOBT and gFOBT respectively) and for advanced adenomas (19.1 and 8.9% for iFOBT and gFOBT respectively). The authors concluded that iFOBT has high sensitivity and specificity for detecting left-sided colorectal cancer and that it may be a useful replacement for the gFOBT.

The study by Dancourt et al. (2008) compared the performance of a 3-day gFOBT and 2-day iFOBT in 17 215 subjects. For 1205 subjects who participated and had colonoscopy, the PPV for the guaiac and immunochemical test was respectively 5.9% v 5.2% for cancer and 27.2% and 17.5% for adenoma.

The study by van Rossum et al. (2008) represents a milestone in the comparison of gFOBT with iFOBT, being the first randomised trial in a population based screening setting. A large number of people (20 623) aged 50–75 years were randomised to either gFOBT (Hemoccult II, *Beckman Coulter Inc. Fullerton, CA, USA*) or iFOBT (OC-Sensor). For iFOBT, the standard cut-off of 100 ng/mL was used. iFOBTs showed higher compliance than did gFOBTs (56.9% vs 46.9% respectively p<.01). The positivity rate was significantly higher in iFOBTs compared to gFOBTs (5.0% vs. 2.4% respectively, p<0.01). Cancer or advanced adenomas were found, respectively, in 11 and 46 of gFOBTs and in 24 and 121 of iFOBTs. The detection rate per 1000 examinations for cancer was 71% higher in iFOBT compared to gFOBT; the detection rate per 1000 examinations for advanced adenomas was 106% higher in iFOBT as compared to gFOBT. The number-to-scope to find 1 cancer or 1 adenoma was comparable between the tests, with the PPV not statistically different. In conclusion, iFOBT compared to gFOBT demonstrated a higher detection rate with a similar PPV.

The results of these five studies are consistent with data from the first European screening pro-grammes. The UK Pilot study adopted Hema-screen, a conventional non-rehydrating gFOBT, using duplicate samples on 3 consecutive stools extended to 2 further sets of 3 stools if indicated. This UK pilot study gave a positivity rate during the first round of 1.9%. The Detection Rates (DR) for cancer and neoplasia (cancer and advanced or non-advanced adenoma) were 1.62 in 1000 and 6.91 in 1000 respectively. The PPV for neoplasia was 46.9% in England and 47.3% in Scotland (UK Colorectal Cancer Screening Pilot Group 2004).

In Italy, a 1-day single sample iFOBT biennial test with positivity cut-off at 100 ng/mL is used in the regional colorectal cancer programmes. The paper by Zorzi that described Italian screening programmes showed a quite different outcome to the UK Pilot study (Zorzi et al. 2008). The positivity rate was relatively high, 5.3% during the first round, the DR for cancer was 3.1 in 1000 (almost two times the UK figure) and the DR for adenoma was 24.7 in 1000 (more than three times the UK result). The PPV for neoplasia was slightly higher than that observed in UK pilot study (54% vs 46.9%) (UK Colorectal Cancer Screening Pilot Group 2004). The Italian programme had adopted a more sensitive (but less specific) strategy compared to the UK.

Hol et al. (2009) recently reported a randomised comparison of gFOBT (Hemoccult II) and iFOBT (OC-Sensor) in a population-based trial in the southwest Netherlands (age 50–74 years). For gFOBT, any 1 of 6 windows collected from 3 stools was designated positive and for iFOBT a single result above a cut-off concentration of 50 ng/mL was designated positive. Test kits were all distributed and returned by mail. Participants with positive results received colonoscopy. gFOBT positivity was 2.8%, and iFOBT positivity was 8.1% at a cut-off of 50 ng/mL, 5.7% at 75 ng/mL, 4.8% at 100 ng/mL and 4.0% at 150

ng/mL. At an iFOBT cut-off concentration of 75 ng/mL, the detection rate for advanced neoplasia was 2x higher than that by gFOBT and was considered to be the optimum cut-off and balance between detection rate and positivity.

4.4.3 Optimising clinical performance using test cut-off limits & algorithms

4.4.3.1 Cut-off limits

Until recently it has not been possible to adjust the analytical sensitivity of FOBT tests. This is still not possible for existing gFOBTs, with the exception of the simple adjunct of hydrating the specimen prior to testing with Hemoccult SENSA. With Hemoccult SENSA, hydration increases test sensitivity at the expense of specificity, thereby increasing the false positive rate (Mandel et al. 1993; Ransohoff & Sandler 2002). Hemoccult and Hemoccult SENSA have been compared in two large studies (Mandel et al. 1993). As a result of rehydration, the rate of positive results increased more than fourfold, from 2.4 to 9.8%. Sensitivity increased from 80.8% to 92.2% while both specificity and PPV decreased (specificity: 90.4% rehydrated and 97.7% non-rehydrated. PPV: 2.2 rehydrated and 5.6 non-rehydrated). In the study by Levin, Hess & Johnson (1997) the positivity rates were 5% and 14.6% and PPV 14% and 7% respectively for the non-rehydrated and the rehydrated. Rehydration using Hemoccult SENSA increases clinical sensitivity and decreases specificity and positive predictive value. The high positivity rate of this approach renders it unsuitable for population screening.

With iFOBTs that provide a numeric result, it is possible to adjust the cut-off limit to obtain an acceptable compromise between clinical sensitivity and specificity. This manipulation can provide an adequate detection rate from an acceptable cohort of subjects invited for colonoscopy. Several recent papers have addressed the issue of modifying the faecal haemoglobin cut-off limit of iFOBTs including the following studies (Sieg et al. 1999; Castiglione et al. 2000; Nakama, Zhang & Zhang 2001; Castiglione et al. 2002; Launoy et al. 2005; Vilkin et al. 2005; Rozen et al. 2006; Chen et al. 2007; van Rossum et al. 2009). The data are summarised in Table 4.5. By increasing the positive cut-off limit, the test sensitivity and positivity rate decreases and specificity and positive predictive values for colorectal cancer detection increase. It must be appreciated that these studies used different commercial products with different analytical characteristics, and therefore simple comparisons can be misleading.

Chen found an analytical cut-off limit range of 100–150 ng/mL faecal haemoglobin in an iFOBT to provide an acceptable balance between sensitivity and specificity (Nakama, Zhang & Zhang 2001; Chen et al. 2007). Increasing the cut-off limit to 300 ng/mL brought an increase in specificity that was small for the corresponding decrease in sensitivity and detection of cancers. A recent study by Rossum of 6157 50–75 year old Dutch participants and using a single OC-Sensor collection and OC-Micro analyser concluded that dropping from the standard 100 ng/mL cut-off to 75 ng/mL brought 'optimal' results and may be recommended for population screening in the Netherlands (van Rossum et al. 2009). This study also concluded that where colonoscopy capacity is insufficient, a cut-off up to 200 ng/mL would result in minimal false negatives for cancer although more for advanced adenoma. Policy makers are faced with an arbitrary decision based on the balance between missed cancers/advanced adenomas and the cost of colonoscopy

4.4.3.2 Number of stool specimens

Several studies have now examined the influence of the number of samples used for testing on clinical sensitivity and specificity. Allison takes any positive result from 3 stool samples measured using FlexSure OBT as an indication for referral and shows higher sensitivity for cancer than studies using

single stool samples (Allison et al. 2007). Unsurprisingly other studies show agreement with that conclusion (St John et al. 1993; Allison et al. 1996; Knaani & Samuel 1997; Nakama et al. 1999; Greenberg et al. 2000; Nakama, Zhang & Fattah 2000; Rozen, Wong et al. 2003). Nakama et al. using Monohaem, showed sensitivities of 89% for cancer with 3 stools compared with 56% for a single stool (Nakama et al. 1999).

Using Hem-SP, Morikawa showed low sensitivity for cancer using a single-day sample (Morikawa et al. 2005). Rozen et al. (2006) used 3 stools for the OC-Sensor which contrasts with 2-day samples used in Japan (Nakama, Zhang & Fattah 2000) and 1-day biennial testing performed in Italy (Castiglione et al. 2002). The relative insensitivity in the Italian study to lesions in the proximal bowel (16.3 vs 30.7%) raises further doubts about the use of a single-day sample. In a study using OC-Sensor in an at-risk population, Levi et al. (2007) took numeric measurements from three samples and used the highest concentration of the three as the discriminating factor. Recent studies have taken the average concentration from 2 stool measurements as the discriminating parameter, an approach that reduces the positivity rate.

The use of different cut-off limits and different numbers of stool samples illustrates how programme algorithms can manipulate clinical sensitivities and specificities for the lesions of interest. Chen describes the use of a cost-effectiveness model as a method of determining the optimal cut-off concentration for an iFOBT (Chen et al. 2007). In the study by Levi et al. (2007) using an iFOBT OC-Micro, a scatter plot of 2 consecutive samples showed that of those with cancer or adenomas, 21 of 91 had elevated or markedly elevated faecal blood in one sample but were normal in the other. This is further evidence of intermittent or variable bleeding, sample heterogeneity or poor sample technique that will reduce clinical sensitivity. Imperiale (2007) commenting on the paper by Levi in his editorial in *Annals of Internal Medicine* (Levi et al. 2007), speculated that concentration-related clinical sensitivity and specificity could be used to determine post-test risk. If risk was related to subject age or sex, this would provide more sophisticated criteria for colonoscopy referral than is currently used.

Guittet et al. (2009b), using a cut-off concentration of 20 ng/mL, reviewed the relative effectiveness of using one sample, one positive from two samples, two positives from two samples or a mean positive from two samples all measured using the Magstream iFOBT. The study concluded that for any sensitivity the mean of two results provided the highest specificity, and at any positivity it provided the highest sensitivity and specificity. It also concluded that one positive from a single specimen was better than one from two specimens and the cut-off should be adjusted to provide an acceptable positivity rate.

A recent paper by Grazzini et al. (2009) looks at the clinical outcome of biennial population screening in 20 596 residents of Northern and Central Italy aged 50–69 years. The study uses OC-Sensor and compares outcomes from strategies using different cut-off limits (80, 100 and 120 ng/mL), one or two samples and referral criteria based on either one positive or two positive results. No strategy is singled out as preferable, although some show limited benefit. Generally, those strategies resulting in more colonoscopy referrals increase the detection rate, particularly for adenomas, decrease the positive predictive value and cost more. At the annual Digestive Diseases Week conference in 2010 van Roon et al. (2010) illustrated the relationship between positivity rate, detection rate, cut-off limits, the number of samples measured and the use of different algorithms for combining the results. For positivity rates between 4% and 9% the user can obtain similar clinical outcomes by changing the cut-off with either one or two samples. The dilemma for a population-screening programme is where to draw the line between detection rates, cost and the inconvenience and morbidity associated with colonoscopy. The study showed no significant reduction in uptake for the two-sample strategy, but it did require the samples to be stored in a refrigerator. The choice is likely to be influenced greatly by both financial and logistical considerations.

Table 4.5: Comparison of clinical performance at different cut-off concentrations

Study	Faecal Hb cut-off (ng/mL)	Nakama, Zhang & Fattah (2000) Japan	Castiglione et al. (2000) Italy (OC-Hemodia)	Castiglione et al. (2002) Italy (Latex aggluti-nation)	Launoy & Berchi (2005) France	Li et al. (2007) Taiwan	Vilkin et al. (2005) Rozen et al. (2006) Israel	Sieg et al. (1999) Germany
Test Positivity (%)	20	-	-	-	5.8	-	-	-
	50	6.5	-	-	3.1	-	-	-
	75	-	-	-	2.0	-	-	-
	100	-	3.5	4.2	-	5.5	-	-
	150	4.1	2.5	3.0	-	-	-	-
	200	-	2.0	2.3	-	-	-	-
	300	3.3	-	-	-	-	-	-
Test Sensitivity (%)	20	-	-		85.0	-	-	-
	50	89	-		68.0-83.0	81.5	79.4	-
	75	-	-		61.0-81.0	-	76.5	-
	100	-	84.0		-	81.5	76.5	-
	150	81	78.9		-	69.2	70.6	87
	200	-	73.4		-	64.6	64.7	83
	300	56	-		-	-	-	78
Test Specificity (%)	20	-	-		94.0		-	-
	50	94	-		97.0		89.7	-
	75	-	-		98.0		93.3	-
	100	-	97.2		-		95.3	-
	150	96	97.2		-		95.9	-
	200	-	97.2		-		96.3	-
	300	97	-		-		-	-
PPV for CRC (%)	20	-	-	-	6.0		-	-
	50	8.6	-	-	9.0		36.0	-
	75	-	-	-	13.0		45.6	-
	100	-	8.8	9.0	-		54.2	-
	150	12.6	11.5	11.6	-		54.5	-
	200	-	13.9	13.4	-		56.4	-
	300	10.8	-	-	-		-	-

4.4.3.3 Sequential testing

Two consecutive diagnostic accuracy studies conducted in Scotland as part of the UK pilot screening study investigated whether testing individuals with positive gFOBT tests using an iFOBT could be more effective in selecting those who should receive colonoscopy (Fraser et al. 2006; Fraser et al. 2007) In both studies the two-tier approach gave very high sensitivities of 95–96% with a negative carrying a less than 1% chance of invasive cancer. The odds ratio for iFOBT positive subjects of having cancer was 7.75 (95% CI 1.84–31.4).

A Chinese study (Li et al. 2006) of 324 subjects who had colonoscopy (mean age 53.5±15.3) showed that an iFOBT following a positive gFOBT had a better specificity for colon cancer detection than gFOBT (94.2% vs. 75.5%), and with similar sensitivity (93.8% and 95.9% vs. 95.9%, p>0.05).

In a multicentre comparison using different FOBT tests on 554 patients referred for colonoscopy (mean age 59.8±11.7), a combination test with a highly sensitive gFOBT (Hemoccult SENSA) and an iFOBT (FlexSure-FS or Hemeselect-HS, *Beckman Coulter Inc. Fullerton, CA, USA*) showed slightly reduced sensitivity but significantly fewer false-positive tests than any single test (Greenberg et al. 2000). The specificity of SENSA/FS (95.7%, p=0.03) and SENSA/HS (95.2%, p=0.07) for the detection of colorectal cancer were each greater than that of any individual test.

4.4.3.4 Participation rate and choice of test

Factors that influence participation rate (uptake) are addressed in Chapter 2 (Sect. 2.4, 2.5.1.1 and 2.5.1.2). Whilst many studies have reported the effect on compliance of different test devices and sampling permutations, some of these are contradictory and many reflect local circumstances. Whilst the analytical methodology, gFOBT vs. iFOBT, will not directly influence compliance, the influence of test methodology on the method of sampling, the number of samples required, a requirement for dietary restriction and the improved clinical outcome will all have a bearing on uptake. The magnitude of the influence will depend on local circumstances. Well-conducted randomised trials have clearly demonstrated that better compliance can be achieved using current iFOBTs than with gFOBTs, but the major influencing factor(s) remain a matter of speculation. In his recent paper Grazzini makes the important observation that, in a biennial screening programme looking for a slow growing adenoma, greater compliance over the long term might be more important than a higher detection rate on a single screen (Grazzini et al. 2009).

4.4.4 Recommendations

Screening algorithm:

- **Sample and test numbers**

  Few studies have examined the number of stool specimens necessary to optimise the diagnostic performance of FOBT. Consideration should be given to using more than one specimen together with criteria for assigning positivity which together provide a referral rate that is clinically, logistically and financially appropriate to the screening programme. The clinical sensitivity and specificity of testing can be modified depending on how the test data are used. Guaiac-based tests typically use 3 stools, but an algorithm using additional tests can be used to adjust clinical sensitivity and specificity (Sect. 4.4.3.2, 4.4.3.1) **(III - C).**[Rec 4.5]

- **Determining test positivity**

  The choice of a cut-off concentration to be used in an immunochemical test to discriminate between a positive and negative result will depend on the test device chosen, the number of samples used and the algorithm adopted to integrate the individual test results. Whilst an increasing number of studies are reporting the experience of different algorithms, local conditions, including the effect on sample stability of transport conditions, preclude a simple prescribed algorithm at this time. Adoption of a test device and the selection of a cut-off concentration should follow a local pilot study to ensure that the chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable (Sect. 4.4.3.1, 4.4.3.2) **(VI - A).**[Rec 4.6]

Maximisation of uptake - Influencing factors associated with the test kit

The choice of the test kit must be influenced by factors that enhance accessibility and uptake (see below and Sect. 4.2.3 and 4.2.4; see also Ch. 2, Rec. 2.14, Sect. 2.5.1.1) **(II - A):**[Rec 4.14]

- **Dietary restrictions**

  In order to enhance participation in screening, test kits should not require dietary restrictions (Ch. 2, Rec. 2.17, Sect. 2.5.1.1; 4.3.2.1 and 4.3.2.3) **(II - A).**

- **Kit design**

  The design of a test kit should make it acceptable to the target population (see Ch. 2, Rec. 2.14, Sect. 2.5.1.1, 4.2.3 and 4.2.4) **(II - A).**

- **Simple and clear instructions**

  A clear and simple instruction sheet should be provided with the test kit (Ch. 2, Rec. 2.16, Sect. 2.5.1.1; Sect. 4.2.3 and 4.2.4) **(V - A).**

4.5 Conclusions

Although it is difficult to draw simple conclusions from the variety of different tests and study settings, we can conclude that iFOBT, in comparison with gFOBT:

- Has no need for dietary restriction;
- Has a major problem with sample instability, and collected samples should *preferably* be kept cool and returned immediately for analysis;
- Provides a greater participation rate than gFOBT;
- Needs a smaller number of stool samples than gFOBT;
- Shows a greater relative sensitivity than gFOBT;
- Shows a greater sensitivity for the detection of advanced adenomas than gFOBT;
- Has a higher recall rate than most gFOBTs;
- Has a PPV similar to those obtained with most gFOBTs;
- Provides an opportunity of using a numeric threshold to find the most appropriate balance between sensitivity and specificity (i.e. between detection rate and positivity to the test); and
- Allows the opportunity to balance recall and detection rates providing each country with the tools to implement a colorectal cancer screening programme that will meet local healthcare expectations within available resources.

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Electronic link to Appendix 1 - Click here*

***The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -**

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

5

Quality assurance in endoscopy in colorectal cancer screening and diagnosis

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Guiding principles for a colorectal screening endoscopy service

1. People undergoing endoscopy, whether for primary screening, for assessment of abnormalities detected in screening, for assessment of symptoms, or for surveillance, should have as good an experience as possible, permitting them to encourage screening, assessment and surveillance of appropriate quality to their friends, family and colleagues.

2. The provision of the service must take into account the perspectives of endoscopists and public health to ensure that the experience is high-quality, safe, efficient as well as person-oriented.

3. Provision of screening should take account of historic development within different local and cultural contexts.

4. The provision of primary screening endoscopy is less complex than follow-up endoscopy (of screen-positives) primarily because of the lower frequency of high-risk lesions in primary screening endoscopy.

5. The introduction of screening must not compromise endoscopy services for symptomatic patients.

6. Screening and symptomatic (diagnostic) services should achieve the same minimum levels of quality and safety.

7. Wherever possible the quality assurance required for screening should have an enhancing effect on the quality of endoscopy performed for symptomatic patients and for other reasons.

8. Screening and diagnosis of appropriate quality requires a multidisciplinary approach to diagnosis and management of lesions detected during endoscopy.

Recommendations[1]

Planning and location of endoscopy services

5.1 When implementing high-volume primary screening endoscopy consideration should be given to locating services in convenient locations for participants **(VI - B).**[Sect 5.1.4]

5.2 Screening services should be provided in proximity to clinical services **(VI - C).**[Sect 5.1.2]

5.3 The planning of screening services should take account of the frequency of high-risk lesions in the screening population and the competencies and equipment required to remove these lesions safely and completely **(III - B).**[Sect 5.1.2]

5.4 The referral rate for excision of high-risk lesions should be audited **(VI - B).**[Sect 5.1.2]

5.5 The clinical lead of the screening service should be satisfied that staff have the necessary competencies, that the equipment is sufficient to perform the necessary procedures and that adverse events can be dealt with effectively **(VI - A).**[Sect 5.1.2]

5.6 Equipment and training needs should be assessed before screening begins **(VI - A).**[Sect 5.1.2]

5.7 The impact of demand from screening on waiting times for symptomatic patients should be assessed to ensure that there is sufficient planned new capacity to avoid inappropriately long waiting times for symptomatic patients **(VI - A).**[Sect 5.1.5]

5.8 Any screening service, regardless of setting, should make an assessment of the risk of adverse events and develop the capability to respond to emergencies **(VI - A).**[Sect 5.1.8]

Infrastructure and equipment

5.9 The infrastructure of an endoscopy unit must include facilities for pre-procedure assessment and recovery, and be designed to allow good patient flow in order to maximise efficiency **(VI - B).**[Sect 5.1.6]

5.10 The environment must have sufficient privacy to maintain the dignity of patients **(VI - B).**[Sect 5.1.6; 5.3.6]

5.11 The volume of equipment should match the demand put upon it to maximise efficiency and avoid patient delays **(VI - B).**[Sect 5.4.3]

5.12 Video endoscopes with the facility for focal application of dye are required for the detection and assessment of high-risk colorectal lesions **(III − B).**[Sect 5.4.3]

5.13 There should be an adequate supply of accessories suited to the endoscopic interventions undertaken within the unit **(VI - B).**[Sect 5.4.3]

5.14 National policies on the use of re-usable accessories should be adopted **(VI - B).**[Sect 5.4.3]

5.15 There should be properly maintained resuscitation equipment in the endoscopy room and recovery area **(VI - B).**[Sect 5.4.3; 5.5.2]

5.16 Maintenance of equipment should be undertaken by competent staff **(V - A).**[Sect 5.4.3]

5.17 There should be regular review of the functioning and cleansing of all endoscopes, according to national or pan-European guidelines containing accepted, published recommendations and standards **(VI - B).**[Sect 5.4.3]

5.18 The results of the review should be available at all times in the endoscopic unit **(VI - A).**[Sect 5.4.3]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

Preparation of the patient and aftercare

5.19 Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (acceptable >90%, desirable >95%). (See also Ch. 3, Rec. 3.16) **(VI - B).**[Sect 5.3.5; 3.3.4]

5.20 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see also Ch. 10, Rec. 10.28) **(III - B).**[Sect 5.3.2; 10.4.3]

5.21 Bowel preparation for screening flexible sigmoidoscopy should involve a single procedure, either enema or oral preparation **(II)**. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and patient preferences should be assessed (see also Ch. 2, Rec. 2.20) **(II - B).**[Sect. 5.3.3]

5.22 To date no single bowel preparation for colonoscopy has emerged as consistently superior over another **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously **(VI - A).**[Sect 5.3.3]

5.23 Several providers of bowel preparation close to the target population should be available when a patient is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation. For flexible sigmoidoscopy screening, organisational options should include the possibility of having the enema administered at the endoscopy unit. (See Ch. 2, Rec. 2.21) **(VI - B).**[Sect 5.3.3]

5.24 Cleansing solution containing mannitol or other malabsorbed carbohydrates (e.g. sorbitol) must be avoided in the preparation of the colon because of the risk of explosion with electrocautery **(III - A).**[Sect 5.4.4]

5.25 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see also Ch. 10, Rec. 10.29) **(VI - B).**[Sect 5.3.1; 10.4.3]

5.26 Before leaving the endoscopy unit, patients should be given a verbal explanation of the results of their procedure; they should also be given written information to support the verbal explanation (see also Ch. 10, Rec. 10.30) **(VI - A).**[Sect 5.5.3; 10.4.3]

5.27 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see also Ch. 10, Rec. 10.31) **(VI - B).**[Sect 5.5.5; 10.4.3]

5.28 There should be pre-defined clinical pathways for individuals found to require further intervention for cancer, including pT1 cancers, incompletely-removed lesions and difficult-to-remove lesions; as well as for incomplete examinations; and for individuals requiring further surveillance. (See Sect. 5.4.4 and Ch. 8, Sect. 8.3.6 and Ch. 9). In addition, failsafe mechanisms must be in place to ensure that these interventions occur **(I - B).**[Sect 5.5.5]

Endoscopic technique

5.29 There should be local policies and processes in place to optimise sedation and patient support in order to maximise tolerance and minimise risk of complications **(I - B).**[Sect 5.4.4]

5.30 Because there is no clear benefit from a particular approach **(I)**, and for practical reasons it is recommended that policies on the use of sedation should be adopted according to protocols based on national or pan-European guidelines, and must take into account historical context, the impact on the patient experience and costs **(I - B).**[Sect 5.1.3]

5.31 Carbon dioxide insufflation is recommended for colonic endoscopic procedures **(I - A).**[Sect 5.4.4]

5.32 Carbon dioxide insufflation should be avoided in patients with COPD, known CO_2 retention or reduced pulmonary function **(VI - A).**[Sect 5.4.4]

5.33 The utilisation of magnetic endoscope imaging (MEI) technology may be considered for patients requiring colonoscopy, particularly when little or no sedation is used **(II - B).**^{Sect 5.4.2}

5.34 The use of variable stiffness colonoscopes is recommended for screening colonoscopy **(I - B).**^{Sect 5.4.2}

5.35 To achieve a high-quality colonoscopic examination it is necessary to perform a complete intubation of the colon and to carefully inspect the mucosa during withdrawal **(I - A).**^{Sect 5.4.5.1}

5.36 If the endoscopist doubts whether he/she is able to remove a high-risk lesion, the lesion must be appropriately documented and, if necessary, its position marked with a tattoo. The patient should then be referred elsewhere to have the lesion removed endoscopically or surgically **(VI - A).**^{Sect 5.1.2}

Performance of endoscopists and quality improvement

5.37 It is recommended that the annual number of procedures performed by an endoscopist is recorded to ensure that the sample size for key performance indicators is sufficient **(III - A).**^{Sect 5.4.5.1}

5.38 Each endoscopist participating in a colorectal cancer screening programme should undertake to perform at least 300 procedures per year to ensure there is a sufficient sample size to assess competence. A higher volume of procedures is desirable **(III - B).**^{Sect 5.4.5.1}

5.39 Services should be planned such that individual endoscopists achieve a desirable volume of procedures (>300/year) **(III - B).**^{Sect 5.1.2; 5.4.5.1}

5.40 There should be auditable photo documentation of completion, preferably a panoramic image of the ileo-caecal valve and caecum, or a video clip with a respective snapshot **(VI - A).**^{Sect 5.4.5.1}

5.41 The unadjusted caecal intubation rate should be a prime indicator of quality of colonoscopy. The acceptable standard is >90%; >95% is desirable (see also Ch.3, rec. 3.11) **(III - A).**^{Sect 5.4.5.1; 3.3.2; 3.3.3}

5.42 There should be documentation and review of reasons for failed completion **(III - B).**^{Sect 5.4.5.1}

5.43 Screening programmes should adopt a minimum set of outcomes to determine the quality of inspection of the colonic mucosa **(VI - A).**^{Sect 5.4.5.1}

5.44 It is recommended that unplanned hospital admission on the same day as the endoscopic procedure be a key adverse outcome. Reasons for admission should be documented **(III - A).**^{Sect 5.4.5.2}

5.45 Endoscopic services must have processes in place to identify and record adverse outcomes occurring after the patient leaves the endoscopy unit **(VI - B).**^{Sect 5.4.5.2}

5.46 All screening programmes should have processes in place for monitoring, auditing, reviewing and acting upon key auditable outcomes and quality indicators **(III - A).**^{Sect 5.2}

5.47 All endoscopists and centres performing endoscopy should participate in a continuous quality improvement programme, including tracking of quality and safety indicators for individual endoscopists. This should include action plans, for both endoscopists and staff, for addressing suboptimal performance **(VI - A).**^{Sect 5.1.7}

Policies and processes

5.48 Decontamination policies and procedures should be compliant with national or pan-European guidelines containing accepted, published recommendations and standards. The policies should be available in the endoscopy department and updated regularly **(VI - A).**^{Sect 5.4.1}

5.49 Decontamination processes should be audited against defined indicators **(VI - A).**^{Sect 5.4.1}

5.50 The endoscopy unit should create and regularly review clinical guidelines, policies and processes, taking into account relevant national or pan-European guidelines **(VI - B).**^{Sect 5.6}

5.1 Effect of screening modality on the provision of endoscopic services for screening

5.1.1 Clinical setting

Colonoscopy is the recommended test for follow-up investigation for individuals who have tested positive with other CRC screening tools (FOBT, Flexible sigmoidoscopy (FS), and also in experimental studies assessing potential screening tools, e.g. DNA faecal markers and CT colonography). High-quality endoscopy (colonoscopy and flexible sigmoidoscopy (FS)) is also used in some Member States as a screening tool for colorectal cancer. The frequency of endoscopy when used as a primary screening tool will be much higher than endoscopy used as a follow-up investigation of another screening test. Thus the phrase 'high-volume screening endoscopy' will be used to refer to endoscopy used as a primary screening tool and 'low-volume screening endoscopy' will be used to refer to follow-up endoscopy. However, it is recognised that if the test positivity rate in a FOBT screening programme is high a large volume of colonoscopies will be generated. The key practical difference of these high- and low-volume populations requiring endoscopy in a screening context is the probability of identifying and nature of high-risk lesions (see below).

The setting in which the endoscopic procedure will be performed will be determined by:

- quality and safety determinants;
- the need for sedation;
- patient-oriented factors;
- possible impact on symptomatic services;
- infrastructure and efficiency;
- staff competencies and equipment; and
- availability of support services.

5.1.2 Quality and safety

Diagnostic procedures, both flexible sigmoidoscopy and colonoscopy, can be performed safely in diverse clinical settings. When providing services for a colorectal cancer screening programme, the key consideration is what facilities and level of competence are required to remove high-risk lesions. Removing large high-risk lesions safely requires a considerable level of competence and appropriate support close at hand when a complication occurs. For example, it would be inappropriate to remove large or difficult high-risk lesions if the colonoscopist is only rarely faced with such a lesion (as in high-volume, low-risk population screening) or if the procedure is being done in a remote setting.

The setting in which screening (or follow-up colonoscopy) is established will be determined by the ability to perform high-quality endoscopy (defined later) and by the probability of finding a high-risk lesion that is difficult to remove completely and safely. If there is concern about removing the lesion it is entirely appropriate for the colonoscopist to leave it (and perhaps tattoo it) and refer the patient on for either endoscopic, or in some instances, surgical excision.

The colonoscopist needs to judge whether he/she is competent to remove a lesion and whether it is safe to remove the lesion in this setting. On the basis of good practice it is recommended that if there is doubt, the lesion must be appropriately documented and the patient referred elsewhere to have the lesion removed **(VI - A).**[Rec 5.36]

Thus, when considering where endoscopic screening services are to be located, the commissioner should be aware of how often a patient may need to be referred elsewhere. If it is expected that referral somewhere else will be a frequent occurrence (perhaps >1% of patients) then it is better to consider locating the service elsewhere, i.e. where the competence of the available endoscopists would permit less referral.

To help in the planning of location of endoscopic services for screening, the following five levels of competency are proposed.

- **Level 0:** The operator does not remove any lesions, referring on all patients with any detected lesions. The operator will be able to biopsy lesions, and pathological material may inform the decision to refer. Basic level of competency for diagnostic FS but not recommended for screening FS.

- **Level 1:** Removing lesions <10 mm in diameter at FS. Rationale: larger lesions will indicate a need for colonoscopy and can be removed when the colonoscopy is performed. Tissue is required from smaller lesions to decide whether colonoscopy is necessary. Thus any person performing FS screening should have this level of competency.

- **Level 2:** Removing polypoid and sessile lesions <25 mm providing there is good access. All colonoscopists should have this level of competency.

- **Level 3:** Removing smaller flat lesions (<20 mm) that are suitable for endoscopic therapy, larger sessile and polypoid lesions, and smaller lesions with more difficult access. Some flat lesions <20 mm with poor access might be unsuitable for this level. Any person doing colonoscopy for positive FOBT in a screening programme should have this level of competency.

- **Level 4:** Removing large flat lesions or other challenging polypoid lesions that might also be treated with surgery. This is the type of lesion that would not be removed at the first colonoscopy because of time constraints, if applicable, or because the surgical option needs to be discussed with the patient. If the patient chooses to have endoscopic therapy, then he/she should be referred to a level 4 competent endoscopist. This level of competency would be expected of only a small number of regionally based colonoscopists.

In the context of colorectal screening and diagnosis in Europe, units only providing Level 0 competencies are not recommended, because unnecessary endoscopic procedures would be required to remove small lesions which could have been removed during the initial FS. Furthermore, unnecessary colonoscopies may be encouraged in the absence of histopathological evaluation of small lesions left in place during the initial FS.

The level of competency to perform high-quality endoscopy and to remove high-risk lesions is also dependent on the competency of the support team and the available equipment: a highly competent endoscopist requires equally competent support staff and the right equipment and supplies to perform the procedure and deal with any problems that might arise (such as clips for uncontrolled bleeding).

It is recognised that the methodology does not currently exist to reliably recognise who has achieved the proposed levels of competence. Thus, until a competency–based assessment process is available the clinical lead of the service should be satisfied that:

- the professionals have the necessary competence;

- the unit has the necessary equipment; and

- in the event of a serious adverse event, it will be possible to manage the patient locally or transfer the patient safely to another institution with the expertise and facilities to care for the patient.

A review of capabilities may identify shortcomings that can be addressed with further training or investment (cross reference to Chapter 6). This training and investment should occur before screening begins.

It is recommended that:

- Screening services be provided in proximity to clinical services **(VI - C).**[Rec 5.2]

- The planning of screening services should take account of the frequency of high risk lesions in the screening population and the competencies and equipment required to remove these lesions safely and expertly **(III - B).**[Rec 5.3]

- Services should be planned such that individual endoscopists achieve a desirable volume of procedures to maintain high competence (>300/year, see section 5.4.5.1) **(III - B).**[Rec 5.39]

- The clinical lead of the screening service should be satisfied that staff have the necessary competencies, that the equipment is sufficient to perform the screening procedures, and that serious adverse events can be dealt with effectively **(VI - A).**[Rec 5.5]

- A review of equipment and training needs should be performed before screening begins **(VI - A).**[Rec 5.6]

- Referral rate for excision of high-risk lesions is an auditable outcome **(VI - B).**[Rec 5.4]

5.1.3   The need for sedation

The use of sedation for lower gastrointestinal endoscopic procedures varies between European countries. Three main patterns are readily discernible:

- infrequent use of sedation;

- frequent use of conscious sedation with opiates and benzodiazepines; and

- almost exclusive use of deep sedation with propofol or general anaesthesia.

This variation suggests there is no perfect approach, and emphasises the need to take into account historic cultural differences when implementing screening endoscopy. A review of the benefits and risks of sedation showed no clear advantage for a particular approach: conscious sedation provides a high level of physician and patient satisfaction and a low risk of serious adverse events with all currently available agents (McQuaid & Laine 2008).

The risk of an adverse cardio-respiratory event is lower if the patient does not have sedation (Eckardt et al. 1999; Rex, Imperiale & Portish 1999; Lieberman et al. 2000; Rex 2000b). Thus, there is less need for monitoring equipment and recovery facilities if sedation is not used. Therefore sedationless endoscopy can occur in more remote settings, and it requires lower set-up costs. However, if no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort. These downsides might affect the uptake and impact of screening: potential screenees are worried about comfort, and incomplete procedures may miss important pathology.

In most circumstances it is possible for the endoscopist to administer conscious sedation, but in some European countries propofol administration requires an attending anaesthetist. Thus the costs of providing sedation, particularly if an anaesthetist is required to administer propofol, will vary between countries. The relative quality and safety of different approaches are reviewed later in this chapter.

Because there is no clear benefit from a particular approach **(I)**, and for practical reasons it is recommended that policies on the use of sedation must be adopted according to protocols based on na-

tional or pan-European guidelines, and take into account historical context, the impact on the patient experience and costs **(I - B).**^{Rec 5.30}

5.1.4   Patient considerations

Patients generally prefer services that are close to home and easily accessible. Thus high-volume screening endoscopy is probably best situated closer to the population to be screened. In contrast, level 3 and 4 expertise for removing high-risk lesions is likely to be provided at district and regional levels respectively. The priority here is the facility and expertise, not proximity.

When implementing high-volume screening endoscopy consideration should be given to locating services in convenient locations for patients to maximise engagement in screening **(VI - B).**^{Rec 5.1}

5.1.5   Possible destabilising effect on symptomatic services

Unplanned introduction of screening endoscopy (at whatever level) creates additional demand and may lead to destabilisation of the symptomatic service. Thus, if endoscopy for screening is introduced alongside symptomatic services, care must be taken to ensue there is sufficient new capacity.

An assessment of the impact of demand from screening on waiting times for symptomatic patients should be made to ensure that there is sufficient planned new capacity such that screening does not lengthen waits for symptomatic patients **(VI - A).**^{Rec 5.7}

5.1.6   Infrastructure and efficiency

The infrastructure requirements for high-volume screening endoscopy need to cater to large numbers of presumptively healthy people. High-volume screening endoscopy requires efficient booking, assessment and recovery processes to function effectively without compromising the patient experience. Thus, it may be advantageous for high-volume screening activities to be separated from routine clinical endoscopy and follow-up endoscopy of screen-positives.

It is self-evident that the infrastructure must be adequate. It must include facilities for pre-procedure assessment and recovery, and must also be designed to allow good patient flow in order to maximise efficiency **(VI - B).**^{Rec 5.9} In addition, a suitable environment will maintain the privacy and dignity of patients **(VI - B).**^{Rec 5.10}

5.1.7   Endoscopist and support staff competencies

Endoscopists and supporting staff providing endoscopy screening must be competent to deliver high quality FS or colonoscopy in order to achieve high patient satisfaction and all the required performance standards relating to quality and safety (see Sect. 5.4.5 and Ch. 6).

It is a fundamental requirement of quality assurance that all endoscopists and centres performing endoscopy should participate in a continuous quality improvement programme, including individual

tracking of quality and safety indicators. This should include management plans, for both endoscopists and staff, for addressing suboptimal quality **(VI - A).**[Rec 5.47]

5.1.8   Support services

Only rarely will a person undergoing a primary screening procedure require admission to hospital for further care. Thus it is not necessary to have medical support facilities close at hand. However, services performing endoscopy in more remote settings must have robust guidelines and processes in place to enable patients to be resuscitated effectively and be transferred rapidly and safely to a hospital where surgical services are available. On this basis it is recommended that any screening service, regardless of setting, should make an assessment of risks and develop the ability to respond to emergencies **(VI - A).**[Rec 5.8]

5.1.9   Conclusion

While there are no absolutes, a case can be made for delivering high-volume screening endoscopy outside traditional hospital settings to improve the patient experience and to reduce healthcare and societal costs. In contrast, risk assessments will indicate that colonoscopy following a positive FOBT or a positive FS is a more complex procedure that is associated with higher risks and should, therefore, be performed in acute hospital settings.

5.2   Audit and quality improvement

This section proposes that endoscopy services monitor key outcomes to ensure that a high-quality and safe service is being provided and to identify areas in need of improvement. Two terms are used for such outcomes: auditable outcomes and quality indicators. An auditable outcome refers to an outcome that should be measured, but for which there is not an evidence base to recommend a standard, such as the comfort of the procedure. A quality indicator is an outcome for which there is a sufficient evidence base to recommend a standard, such as caecal intubation rate.

It is expected that some auditable outcomes will become quality indicators as the evidence base improves, and that the standards of quality indicators will rise as standards improve.

On the basis of this, it is recommended that all screening programmes should have processes in place for monitoring, auditing, reviewing and acting upon key auditable outcomes and quality indicators in the following areas (see also Annex 5.1 and 5.2 and Chapter 3) **(III - A):**[Rec 5.46]

- Quality;
- Safety; and
- Patient feedback

5.3   Before the procedure

Beginning the patient journey

Section 5.3 and subsequent sections follow the patient journey from invitation to discharge from the endoscopy service.

5.3.1   Patient information and consent

Information in this context includes information related to the endoscopic procedure and should include why the procedure is being done, what it involves, preparation for the procedure, and the risks. The patient should be told what he/she might expect to happen after the procedure (including contact details in case of emergency) and the plan of aftercare. The patient should be informed about the options for sedation and how this might affect their perception of the procedure and the associated restrictions on travelling home. There are subtle differences in the approach to consent between a primary screening test and one done following a positive screening test such as FS and FOBT, explained in more detail in Chapter 10.

The consent process involves an explanation of the procedure, the potential benefits, the risks and possible consequences. Consent for endoscopic procedures begins with a recommendation to have the examination, and ends when the procedure is complete. The individual must have the opportunity to withdraw consent at any stage during this process.

It is good clinical practice for an endoscopy service to have policies that guide the consent process, including a policy on withdrawal of consent immediately before or during the endoscopic procedure. **(VI – B).**[Rec 5.25]

The key elements of patient information for endoscopy include:

- considerations related to current medications including anticoagulants and antiplatelet agents;

- considerations related to previous medical illnesses;

- the benefits of the test;

- how to prepare for the procedure (including bowel cleansing);

- the nature of the procedure and what it involves;

- possible adverse events including discomfort and complications;

- what support the patient may need after the procedure, particularly if they are sedated; and

- the importance of not driving or making important decisions after sedation.

Auditable outcomes: patient feedback on information and consent processes. These assessments should ideally be both qualitative and quantitative and make an assessment of the patient experience judged by the gap between the expectation and actual experience (see Chapter 3). Withdrawal of consent should be registered as an adverse clinical incident.

5.3.2 Pre-assessment

The purpose of pre-assessment is to identify factors that might influence the outcome of the procedure, such as anticoagulation and general health status. Pre-assessment also provides an excellent opportunity to ensure the patient understands the bowel cleansing process and to answer any questions the patient may have.

The nature of the pre-assessment will depend on whether there has been prior contact with an endoscopy service health professional. If there has been no prior contact with the service, it is advised to pre-assess the patient several days before the procedure, at least before starting bowel cleansing. This will enable the procedure to be rescheduled if there are concerns about safety, or for medication such as warfarin to be withdrawn in sufficient time to allow its anticoagulant effect to wear off.

Available evidence (Bini et al. 2003; Hui et al. 2004; Bernstein et al. 2005; Harris et al. 2007a; Lee et al. 2008; Tsai et al. 2008) suggests that the following patient-related variables should be identified and taken into account prior to FS or colonoscopy because they can be associated with more adverse events, longer duration, and incomplete examination: **(III)**

- Use of anticoagulants e.g. warfarin;

- Anatomy (female sex);

- Age of patient;

- Prior abdominal surgery;

- BMI;

- Diverticular disease;

- ASA PS (American Society of Anesthesiology classification of Patient Status)[2] and information that may influence type and level of sedation (for those procedures where sedation may be used); and

- Presence of risk factors for endocarditis

On the day of the procedure there should be a brief review of the previously collected information and measurement of basic cardio-respiratory function

It is recommended that each endoscopy service have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be paperwork and processes in place to support the policy **(III - B).**[Rec 5.20]

Auditable outcomes: Recording and review of adverse clinical events related to inadequate pre-assessment (e.g. anticoagulants not stopped or risk factors for endocarditis not identified)

5.3.3 Colonic cleansing

Inspection of the colon requires careful preparation removing colonic contents to optimise the safety and quality of the procedure. Ideally there should be no residual stool or liquid in the lumen that could mask any suspicious area.

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[2] The American Society of Anesthesiology classification of Patient Status (ASA PS) groups patients into 6 categories based on an assessment of their physical condition prior to an invasive procedure: (http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx)

Flexible sigmoidoscopy

The ongoing European sigmoidoscopy trials adopted a bowel preparation based on a single enema, self-administered at home within two hours from the appointment, or, in one case, at the screening centre.

No studies were found assessing the effect of having the enema performed directly at the screening centre, although this represents an option that might enhance participation by reducing patient's concerns and enhancing engagement. Available evidence from one controlled trial did not indicate that using two enemas (the first the night before the test and the second two hours before the scheduled time for the exam) affects participation compared to using a single enema (Senore et al. 1996). Oral preparation was associated with a reduced participation in a large screening trial, compared to enema (Atkin et al. 2000). Adding oral preparation to the enema resulted in reduced participation (Bini et al. 2000).

No difference in the proportion of inadequate exams was observed when comparing a single enema regimen to a preparation using two enemas or to oral preparation.

Bowel preparation for screening sigmoidoscopy should involve a single procedure, either enema or oral preparation **(II)**. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and patient preferences should be assessed (see also Ch. 2, Rec. 2.20) **(II - B).**[Rec. 5.21]

Colonoscopy

Data on the impact of different preparation regimens in the context of population screening with colonoscopy are lacking. A recent systematic review concluded that no single bowel preparation emerged as consistently superior. Sodium phosphate was better tolerated (Belsey, Epstein & Heresbach 2007), but safety alerts on its use have recently been issued by the US FDA and Health Canada. The authors identified a general need for rigorous study design to enable unequivocal conclusions to be drawn on the safety and efficacy of bowel preparations.

Timing of administration of the recommended dose appears important, as it has been established that split dosing (the administration of at least a portion of the laxative on the morning of the examination) is superior to dosing all the preparation the day before the test, both for sodium-phosphate and polyethylene glycol (Aoun et al. 2005; Parra-Blanco et al. 2006; Rostom et al. 2006; Cohen 2010) **(II).**

A systematic review (Belsey, Epstein & Heresbach 2007) of different bowel cleansing regimens identified no significant differences other than improved patient tolerance of sodium picosulphate preparations. Furthermore, there are no preferred methods of assessing the effectiveness of bowel cleansing. Care must be taken however with some agents (i.e. phospho prep) in certain patient groups, especially the elderly and those with renal failure, due to potential renal side effects (WHO 2009) **(I)**.

See also Chapter 2 (Sect. 2.5.2.2, 2.5.2.3) for literature review about bowel preparation for FS and colonoscopy, and for organisational aspects.

To date no single bowel preparation for colonoscopy has emerged as consistently superior over another **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see also Ch. 2, Rec. 2.22) **(VI - A).**[Rec 5.22]

Auditable outcome: Quality of preparation, patient satisfaction with the bowel cleansing regimen.

Accessibility

Several providers of bowel preparation close to the target population should be available when a patient is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation. For sigmoidoscopy screening, organisational options include the possibility of having the enema administered at the endoscopy unit. (See Ch. 2, Rec. 2.21) **(VI - B).**[Rec 5.23]

5.3.4   Scheduling and choice

Booking processes must be robust to minimise late cancellations and failures to attend. To increase the chance of attendance an invitation for a primary screening test should be sent 2–3 weeks before the procedure is due, with an option for the patient to change the appointment if it is not convenient (see section 2.4.3.1).

Auditable outcome: Patient feedback on booking processes.

5.3.5   Timelines

A timely procedure is not critical in the context of primary screening but it is very important when endoscopy is performed following a previous positive screening test. A delayed procedure may not be critical biologically, but it can cause unnecessary anxiety for the screenee.

To ensure that patient anxiety is not unnecessarily increased, it is recommended that follow-up colonoscopy after positive screening be performed as soon as reasonably possible, but no later than within 31 days of referral (acceptable >90%, desirable >95%) (see also Ch. 3, Rec. 3.16, Sect 3.3.4) **(VI - B).**[Rec 5.19]

Auditable outcome: Time taken from positive screening test to secondary endoscopic examination. If further pathological information is required before the decision to perform a colonoscopy, then the maximum and the desirable targets of four and two weeks, respectively, should be timed from the receipt of the pathology report. The pathology report should be delivered to the screening programme within two weeks.

5.3.6   Environment

The environment should be conducive to a good experience and efficient processing. It should be physically comfortable, offer privacy and there should be facility to hold private conversations with screenees and their relatives. The reception and assessment areas should be separate from recovery facilities **(VI - B).**[Rec 5.10]

Auditable outcomes: patient feedback on environment and patient turn around times.

5.4   During the procedure

There is an increasing body of evidence demonstrating unacceptable miss rates of cancer following colonoscopy. Miss rates vary between endoscopists suggesting that care with the examination and technique play a key role in ensuring cancer is not missed.

Endoscopists must have a mix of technical, knowledge and judgement competencies to identify and successfully remove high-risk lesions. Ideally they will perform a complete examination quickly, safely and with minimal discomfort, leaving time to properly inspect the colon, and safely remove and retrieve lesions. They will identify all abnormal areas, characterise them and make a judgement of what to do. They will then, if it is appropriate to do so, safely remove and retrieve all neoplastic lesions

Providing such high-quality and safe endoscopy requires a team approach with appropriate equipment immediately to hand. The nursing support team must ensure the patient is comfortable and has stable observations to allow the endoscopist to devote his attention to the procedure. The nurses also provide important technical support ensuring endoscopy equipment is serviceable and that all the necessary accessories are readily available. Finally they play an important role supporting the endoscopist during therapeutic procedures. Both endoscopist and nurse should regularly reflect on their practice together with pathology and surgical teams in order to optimise patient outcomes.

High-quality and safe endoscopy also depends on adequate maintenance of equipment, and on an adequate supply of accessories for the range of procedures undertaken in the department. This should include equipment to manage complications of excision of high-risk lesions such as bleeding and in some instances, perforation. Endoscopy equipment is expensive and is subject to frequent and occasionally heavy use. It is essential that equipment be maintained by competent staff. Maintaining and repairing old endoscopic equipment is often more expensive than replacing it.

It is not appropriate for this chapter to provide a manual of how to perform colonoscopy and detect and remove high-risk lesions. However, there have been significant advances in decontamination processes, technique and technology in recent years. Because these advances might affect service provision and patient outcomes, it is considered important to review the evidence for their effectiveness.

Technological improvements have promised easier insertion of endoscopes and better visualisation of the mucosa. However, despite the potential of advances in endoscopic technology, they cannot be recommended for routine use until they have been demonstrated to be of benefit in clinical practice. The following sections provide an overview of the current state of these technologies and best practice for safe, high-quality endoscopy.

5.4.1   Cleansing and disinfection

Patients need to be reassured that decontamination processes are up to date and effective. Guidelines on cleaning and disinfection of endoscopes and endoscopic devices have been developed by the ESGE-ESGENA[3] (Beilenhoff et al. 2007; Beilenhoff et al. 2008).

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[3] ESGE-ESGENA: European Society of Gastrointestinal Endoscopy - European Society of Gastroenterology and Endoscopy Nurses and Associates.

It is recommended that decontamination policies and procedures be compliant with national or pan-European guidelines based on accepted, published recommendations and standards and should be audited against defined indicators. The policies should be available in the endoscopy department and updated regularly **(VI - A).**[Rec 5.48, 5.49]

Auditable outcomes: Defined by national or European guidance.

5.4.2   Kit - technologies for improving insertion of the colonoscope

A variety of endoscope technologies may facilitate caecal intubation and improve patient tolerance. These include variable stiffness instruments, magnetic tracking devices and wire-guided techniques.

A recent meta-analysis (Othman et al. 2009) of variable stiffness colonoscopes identified seven randomised trials involving 1923 patients: four trials comparing adult variable stiffness colonoscopes with standard adult colonoscopes in adults, and three evaluating the paediatric variable stiffness colonoscope. The caecal intubation rate was higher with the use of variable stiffness colonoscopes. The variable stiffness colonoscope was associated with lower abdominal pain scores and decreased need for sedation during colonoscopy. Intubation times were unaffected by the variable stiffness colonoscope **(I).** The use of variable stiffness colonoscopes is recommended for screening colonoscopy **(I - B).**[Rec 5.34]

The present bibliographic search did not yield any relevant publications on improvement of completeness of colonoscopy through wire-guided techniques. This new technology has been investigated in endoscopic management of obstructive tumours (Ramadori, Lindhorst & Armbrust 2007).

Two RCTs of the magnetic endoscopic imaging (MEI) device showed improved performance of endoscopists, both with variable stiffness colonoscopy and with traditional colonoscopy, in terms of patient tolerance and caecal intubation rates, in particular when little or no sedation is used (Shah et al. 2000; Shah et al. 2002) **(II)**. The utilisation of magnetic endoscope imaging (MEI) technology may be considered for patients requiring colonoscopy, particularly when little or no sedation is used **(II - B).**[Rec 5.33]

5.4.3   Kit – techniques and technologies to enhance detection, characterisation and removal of high-risk lesions

Image enhancing techniques and technology promise to improve management of high-risk lesions in three ways.

1. First, they might improve the detection of lesions. This will only add value if the lesions detected are important biologically: identifying more biologically unimportant lesions will add workload and risk.

2. Second, they might better define the margins of the lesion to help the endoscopist ensure that it is completely excised.

3. Third, they might help characterise the nature of the lesion, helping the endoscopist decide whether to remove it. This third aspect is of critical importance because it might be more appropriate not to remove the lesion because of an increased risk of malignancy. Alternatively, if an endoscopist can safely leave lesions that do not need to be removed, such as small hyperplasic polyps, considerable time could be saved and small risks of polypectomy avoided.

Essentially there are two approaches to enhanced lesion recognition and characterisation: dye-spraying or chromoendoscopy, and image manipulation techniques or image-enhancing technology.

Chromoendoscopy

Widespread application of dye to the lumen of the colon (pan-chromoendoscopy) improves the detection of diminutive lesions (Brown, Baraza & Hurlstone 2007) **(I)**. However, pan-chromoendoscopy is time consuming and the extra lesions detected may be unimportant clinically as a significant number of diminutive lesions may regress (Rother, Knopfle & Bohndorf 2007). The authors of a recent Cochrane review concluded that *selective application* of dye to suspicious areas (selective chromoendoscopy) may be more appropriate during colonoscopy **(VI)**.

This approach is consistent with the conclusions of a recent international workshop which reviewed the role of non-polypoid lesions in the aetiology of colorectal cancer. The endoscopist should be skilled in recognising subtle changes in the appearance of the mucosal surface, particularly alterations in colour, vascularisation and morphology, to identify suspicious areas requiring dye spraying and to better detect polypoid lesions. Small patches of mucus may require rinsing to expose underlying suspicious areas worthy of staining, particularly in the right colon (Kudo et al. 2008).

Selective chromoendoscopy with dye spraying on the lesion has been shown to be superior to conventional colonoscopy predicting polyp histology (Pohl et al. 2008) **(III)**. Magnification chromoendoscopy is more effective than conventional chromocolonoscopy for diagnosing neoplastic colorectal polyps (Emura et al. 2007) **(II)**.

Expert opinion **(VI)** suggests that selective chromoendoscopy facilitates:

- assessment of the lesion and its borders;
- excision of the lesion and of residual tissue;
- colonoscopy for patients with chronic inflammatory bowel disease; and
- colonoscopy for high-risk family syndromes such as HNPCC.

Thus for most polypoid and non-polypoid colorectal abnormalities, a flexible high-definition video endoscope and the facility for selective application of dye (chromoscopy) to the lesion is currently sufficient for detection and characterisation of high-risk lesions. It is recommended that all but the smallest flat or sessile lesions be 'lifted' with submucosal injection of saline or colloid to facilitate safe removal (endoscopic mucosal resection). Lesions that do not 'lift' should not be removed because they are more likely to be malignant, and removal is more likely to lead to perforation **(VI)**.

Image enhancing technology

There is conflicting evidence regarding the potential for narrow band imaging (NBI), Fuji Intelligent Chromo Endoscopy (FICE), and other techniques of image processing commonly referred to as "virtual chromoendoscopy" to improve detection and characterisation of high-risk lesions. One trial showed an increase in the detection rate of diminutive adenomas (Inoue et al. 2008). There was no difference in adenoma detection rates using NBI technique compared to white-light colonoscopy reported by other published trials (Johanson 2006; Rex 2006; Kaltenbach et al. 2008; Kaltenbach, Friedland & Soetikno 2008; Adler et al. 2009) **(II)**.

The use of autofluorescence was associated with a higher polyp detection rate compared with conventional endoscopy in one study, although the observed improvement was mainly attributable to an increased diagnostic yield of diminutive adenomas (Matsuda et al. 2008; Mayinger et al. 2008; McCallum et al. 2008) **(II)**.

Studies comparing the performance of colonoscopy with high definition versus standard colonoscopes did not show an increase in the detection rate of adenomas or hyperplastic polyps when using high-definition instruments (East et al. 2008; Pellise et al. 2008; Burke et al. 2009) **(II-III)**.

The results of diagnostic accuracy studies showed better accuracy of NBI colonoscopy compared to standard colonoscopy in differentiating between neoplastic and non-neoplastic lesions (Su et al. 2006; Katagiri et al. 2008) **(III)**. In the recent Cochrane review of chromoendoscopy, it was suggested that NBI may become the gold standard in enhanced techniques for detection of colorectal lesions, but with the advantage of reduced procedure time compared to chromoendoscopy. One trial comparing diagnostic accuracy of NBI with chromoendoscopy on 99 Patients has been retrieved (Tischendorf et al. 2007). The study did not find a significant difference in accuracy between the two technologies for the differentiation of neoplastic vs. non−neoplastic lesions. Further trials comparing NBI and chro-moendoscopy are needed.

Further experience and evidence about efficacy, benefits and potential adverse effects, as well as cost-effectiveness, are required before additional technologies can be recommended for routine, pan-European use in colorectal cancer screening and diagnosis. Particularly in the screening context, improvements in detection and diagnosis may be accompanied by unacceptable decreases in specificity, and/or disproportionate, unacceptable increases in cost, measured both in human and financial resources.

After sufficient standardisation of procedures and protocols in feasibility studies, pilot studies conducted in the framework of population-based screening programmes, and based on a randomised public health policy, could provide appropriate evidence to justify future recommendations for widespread implementation of new technologies.

In view of the above it is recommended that:

- The provision and maintenance of equipment in the endoscopic unit should be carefully managed based on local guidelines that comply with relevant national and pan-European guidelines containing accepted, published recommendations and standards.

- Flexible video endoscopes and the facility for focal application of dye to the lesion should be used in colorectal cancer screening **(III — B).**[Rec 5.12]

- The volume of equipment should match the demand put upon it to maximise efficiency and avoid patient delays **(VI - B).**[Rec 5.11]

- There should be an adequate supply of accessories suited to the endoscopic interventions undertaken within the unit **(VI - B).**[Rec 5.13]

- Use of re-usable accessories should be based on national policy **(VI - B).**[Rec 5.14]

- There should be properly maintained resuscitation equipment in the endoscopy room and recovery area **(VI - B).**[Rec 5.15]

- Maintenance of equipment should be undertaken by competent staff **(V - A).**[Rec 5.16]

- There should be regular review of the functioning of all endoscopes, in accordance with manufacturer specifications and instructions and relevant national or pan-European guidelines **(VI - B).**[Rec 5.17]

- The results of the review should be available at all times in the endoscopy unit **(VI - A).**[Rec 5.18]

5.4.4 Sedation and comfort

Flexible sigmoidoscopy

Although flexible sigmoidoscopy is not currently recommended by the EU for colorectal cancer screening, previous results of ongoing trials indicate that screening is feasible and the procedure is well accepted by screenees (UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Segnan et al. 2005; Weissfeld et al. 2005; Segnan et al. 2007; Hoff et al. 2009). No sedation for FS was used in these studies **(I)**.

Colonoscopy

Colonoscopy can be an uncomfortable and distressing experience. These adverse effects can be reduced by careful patient preparation and sedation. As mentioned previously in this chapter, there are widely differing practices of sedation for endoscopy in the EU that reflect historic practice and cultural differences.

Sedation improves patient tolerance of colonoscopy, particularly sedation using propofol combined with other sedative agents such as midazolam and analgesics such as pethidine and fentanyl (McQuaid & Laine 2008) **(I)**. However, excessive sedation is considered to be an important contributor to cardio-respiratory related deaths following endoscopy in high-risk patients, particularly the elderly.

According to Rex (Rex 2000b), most of the risk of colonoscopy is related to sedation. Cardio-respiratory complications are infrequent for patients without known heart or lung disease, but monitoring of oxygenation and blood pressure should be performed for all sedated patients.

Although hypoventilation, cardio-pulmonary events and vasovagal reactions may be related to pain and distension caused by the endoscopic procedure, in most cases they are more closely associated with the use of sedatives and opioids. Reduction in risk for these reactions has been observed in a study aimed to determine the incidence of such events when sedation is given only as required. All procedures in this study were performed by senior gastroenterologists with optimal equipment and nursing staff. Patients undergoing colonoscopy without sedation had less decline in blood pressure and fewer hypoxic episodes than sedated patients (Eckardt et al. 1999) **(V)**.

Heavily sedated patients are more difficult to turn, and this may compromise caecal intubation and mucosal visualisation **(V)**.

The available evidence indicates that the quality and safety of colonoscopy in patients that receive propofol sedation is comparable to that in patients receiving light, conscious sedation (or no sedation), provided patients given sedation are assessed properly prior to their procedure (McQuaid & Laine 2008; Singh et al. 2008) **(I)**.

Propofol seems to be better than benzodiazepines or narcotics on recovery, discharge time and patient satisfaction and equivalent on procedure time, caecal intubation rate and adverse events **(I).** However, in many countries an anaesthesiologist is required for propofol administration.

It is recommended that there be local policies and processes in place to optimise sedation and patient support in order to maximise tolerance and minimise risk of complications **(I - B).**[Rec 5.29]

The following categories and data relevant to sedation should be monitored:

1. No sedation;

2. Conscious sedation and substances used;

3. Propofol sedation or general anaesthesia, and substances used; and

4. Insufflation gas: air or CO_2 (see below).

Auditable outcomes: Sedation levels, patient feedback on comfort, dignity and privacy, and adverse incidents related to sedation, including use of reversal agents.

Carbon dioxide insufflation

Gas insufflation is mandatory to ensure good visualisation during colonoscopy. Currently, air is commonly used for this purpose (Janssens et al. 2009). However, significant amounts of air can be retained in the GI tract (Bretthauer et al. 2003) causing pain and discomfort for the patient. Pain associated with colonoscopy has been identified as a major barrier to participation in CRC screening (Denberg et al. 2005; Condon et al. 2008; McLachlan, Clements & Austoker 2009).

Randomised trials have shown that carbon dioxide insufflation significantly reduces abdominal pain and discomfort in patients undergoing colonoscopy and flexible sigmoidoscopy (Bretthauer et al. 2002a; Bretthauer et al. 2002b; Sumanac et al. 2002; Church & Delaney 2003; Wong et al. 2008) **(I)**.

Side effects of $CO2$ insufflation were not detected in unsedated patients in two randomised studies identified in the present literature search and involving 350 patients (Bretthauer et al. 2002b; Bretthauer et al. 2005). Slightly elevated end-tidal CO_2 levels were detected in sedated patients in the latter study, but only 52 sedated patients were included in the study and patients with chronic obstructive pulmonary disease, as well as patients with known CO_2 retention, were excluded.

Since carbon dioxide is an inert gas that cannot form a combustible mixture with hydrogen and methane, CO_2 insufflation will avoid the very rare risk of explosion during sigmoidoscopy or colonoscopy (see below).

Following incomplete colonoscopy, an alternative examination is frequently required. Provided adequate facilities are available, same-day CT or MRI colonography, or, in appropriate cases, double-contrast barium enema would be desirable. However, same-day radiologic examination following colonoscopy frequently yields suboptimal quality when air insufflation is used for colonoscopy, due to retained air in the colon. If CO2 insufflation has been used, same-day radiologic imaging is generally feasible with appropriate quality. This avoids the necessity of scheduling the additional radiologic examinations on another day and further colon cleansing (Phaosawasdi et al. 1986; Rodney, Randolph & Peterson 1988) **(III).**

In light of the above evidence and considerations:

* Carbon dioxide insufflation is recommended for colonic endoscopic procedures **(I - A).**[Rec 5.31]

* Carbon dioxide insufflation should be avoided in patients with COPD, known CO_2 retention or otherwise reduced pulmonary function **(VI - A).**[Rec 5.32]

Risk of explosion from electrocautery during air insufflation of the colon

Oxygen in room air, insufflated during colonoscopy, has been shown to react with colonic hydrogen and methane gas to produce a combustive gas mixture (Bigard, Gaucher & Lassalle 1979). A recent review found 20 cases of colonic explosion during electrocautery published since 1952 and confirmed that colonic gas explosion is a rare, but potentially lethal complication during colonoscopy with electrocautery (Ladas, Karamanolis & Ben-Soussan 2007).

Accumulation of colonic combustible gases at potentially explosive concentrations due to inadequate colon preparation and use of air, rather than a non-inert gas such as carbon dioxide for insufflation are the principal causes of gas explosion. Fifteen of the 20 reported cases were associated with bowel preparation using malabsorbable, fermentable carbohydrates (14 cases with mannitol, which is no longer commonly used in colonoscopy, and one with sorbitol). The five other cases involved argon

plasma coagulation for post-radiation colitis. Cleansing solution containing mannitol or other malabsorbed carbohydrates (e.g. sorbitol) must be avoided in the preparation of the colon because of the risk of explosion with electrocautery **(III - A).**[Rec 5.24]

5.4.5   Endoscopist techniques and performance

There is ample evidence of varying performance of endoscopists and, as a consequence, varying outcomes for patients in endoscopy (Bressler et al. 2007; Dafnis et al. 2001; Enns 2007; Shah et al. 2007; Rabeneck et al. 2008; Singh et al. 2009) **(III)**.

High-quality and safe endoscopy is critical for the success of screening therefore it is vital to have continuous monitoring of performance. Performance can be assessed by measuring outcomes that directly affect the patient or surrogate outcomes that are linked with true patient outcomes. Examples of outcomes that directly affect the patient are discomfort, reduced probability of developing cancer, perforation and interval cancer. Examples of surrogate outcomes include caecal intubation rates, withdrawal times and adenoma detection rates.

Very often it is difficult to identify true patient outcomes and link them with individual performance such as missed cancer or reduced risk of cancer. Thus, surrogate outcomes are relied on for assessing individuals. Given limitations on the volume of procedures that a competent endoscopist can regularly perform, the frequency with which an event occurs will affect the ability of a measure to determine individual performance. If the event rate is high (such as adenoma detection), relatively small numbers suffice to assess performance. In contrast, if the event rate is low (such as perforation), very large numbers of procedures are required to assess professional performance.

If there are concerns about performance, or if there is a desire to assess competence prior to participation in a screening programme, it is possible to assess knowledge and skills-based competencies in addition to reviewing key performance indicators (Barton 2008). This approach may become particularly important for assessing skills, knowledge and judgments associated with excision of high-risk lesions once a competency framework has been created.

5.4.5.1 Quality outcomes

The quality of a colonoscopic examination is not only dependent on complete intubation of the colon. Careful and complete visualisation of the mucosa during withdrawal is equally important (Brown, Baraza & Hurlstone 2007) **(I - A).**[Rec 5.35] The following quality indicators should be monitored for each endoscopist to secure good quality of the examination:

Documentation of consent

Prior informed consent should be documented for every examination. Fail-safe mechanisms should be in place to assure that the endoscopist does not conduct a procedure for which prior consent is not documented. Any exceptional cases in which prior consent is not provided should be documented and reviewed.

Numbers of procedures

There is evidence that endoscopic proficiency increases with the number of procedures performed (Enns 2007). Furthermore, low numbers of procedures are associated with a greater risk of complications: the lowest complication rate in a population-based study of outpatient colonoscopy was associated with the highest number of procedures (more than 300 per endoscopist per year; (Rabeneck et

al. 2008; Singh et al. 2009)). However, performing a large number of procedures is not sufficient proof of competency; bad habits can persist even in very experienced endoscopists.

As already mentioned, large numbers are required to provide accurate estimates of performance, particularly if events are infrequent. The 95% confidence interval for a completion rate of 90% for 150 procedures per year is 85–95%; the interval for 300 procedures per year is 87–93%.

It is recommended that the annual number of procedures performed by each endoscopist be recorded to ensure that the sample size for other performance indicators is sufficient **(III - A).**[Rec 5.37]

Although the number of procedures performed annually is not a reliable measure of quality, achieving an adequate volume is essential to maintaining skills and effectively monitoring performance. It is therefore recommended that each endoscopist participating in a colorectal cancer screening programme should undertake to perform at least 300 procedures per year. A higher volume of procedures is desirable to maintain high quality **(III - B).**[Rec 5.38]

Services should be planned such that individual endoscopists achieve a desirable volume of procedures (>300/year) **(III - B).**[Rec 5.39]

Insertion to caecum and withdrawal time

Rapid insertion of the colonoscope is a proxy indicator of technical performance of colonoscopy, provided comfort levels are satisfactory and complication rates are not elevated. Rapid insertion leads to greater efficiency but particular caution should be observed in heavily sedated patients. Withdrawal time is a proxy for careful inspection of the mucosa (see below). If adenoma detection rates are low and withdrawal times short, endoscopists should be encouraged to withdraw more slowly.

Documentation of completion of colonoscopy

Only one study was retrieved assessing specificity and sensitivity of a pair of photographs to assess the completeness of colonoscopy, using a video-clip as the reference standard. The study found a sensitivity of 51.4% and a specificity of 89.2% which were considered too low to be used for reliably documenting colonoscopy completion (Thuraisingam, Brown & Anderson 2008). A single panoramic shot showing both the ileo-caecal valve and the caecum may improve sensitivity **(VI)**.

While ileal intubation is not required in the context of colorectal screening, a picture of ileal mucosa provides strong evidence of completion. Taking ileal biopsies to document completion is discouraged, however, because of concern about transmission of variant Creutzfeldt-Jakob Disease (CJD). Also, intubation of the ileum takes extra time and effort.

It is therefore recommended that completion be documented by auditable photo documentation: preferably a panoramic image of the ileo-caecal valve and caecum, or a video clip with a respective snapshot **(VI - A).**[Rec 5.40]

Completion rates

Caecal intubation rate is one of the key quality indicators of colonoscopy. Caecal intubation rates are affected by a number of factors including age, sex, low BMI, bowel cleansing, sedation, diverticular disease and general health status (Eloubeidi et al. 2003; Rathgaber & Wick 2006; Harris et al. 2007b; Segnan et al. 2007; Radaelli et al. 2008; Viiala & Olynyk 2008).

It can be expected from this evidence that it is possible to achieve a higher caecal intubation rate in patients attending for average risk screening than those attending for investigation of symptoms. US guidelines recommend a different intubation rate standard for screening and for symptomatic populations: 95% and 90%, respectively (Rex et al. 2002). Adjusted completion rates (for factors such as bowel prep or obstruction) are open to diverse interpretation, and it is recommended to use

unadjusted rates for the standard. The exception to this would be an obstruction leading to operative intervention. This is a clear-cut reason for adjusting the rate.

It is recommended that unadjusted caecal intubation rate (as defined above) be a prime indicator of quality of colonoscopy The acceptable standard is >90%; >95% is desirable (see also Ch. 3, Rec. 3.11, sect 3.3.2 and 3.3.3) **(III - A).**[Rec 5.41] There should be documentation and review of reasons for failed completion **(III - B).**[Rec 5.42]

Complete and correct identification of neoplastic lesions

The principal aim of screening FS and colonoscopy is to identify and, in appropriate cases, remove neoplastic lesions in order to lower the burden of colorectal cancer in the population.

Furthermore, a complete colonoscopy that has identified all the relevant pathology is a prerequisite for assessing future risk for inclusion in colonoscopy surveillance programmes (see Chapter 9). There is good evidence of varying rates of detection of high-risk lesions and of missed lesions in back-to-back colonoscopy studies (Rex et al. 1997). Rapid withdrawal at colonoscopy is associated with lower adenoma detection rates (Rex 2000a; Barclay et al. 2006; Millan et al. 2008). Internationally accepted guidelines on performance indicators of colonoscopy recommend monitoring direct or proxy markers of detection of suspicious lesions: polyps, adenomas or withdrawal times (Rex et al. 2002; Levin et al. 2005). In a recently published retrospective study based on data from a colonoscopy screening programme with a high percentage of participants with a family history of colorectal cancer, adenoma detection rate has been shown to be an independent predictor of interval cancer (Kaminski et al. 2010).

Counting polyps is relatively easy but capturing adenoma detection rates can be problematic if endoscopy and pathology databases are not linked. Withdrawal times are a proxy measure and inferior to measuring detection of polyps or adenomas.

There are now well-defined criteria for high risk and the evidence base underpinning these criteria is discussed in Chapter 9. It is recommended that these criteria be used as a marker of careful inspection of the colonic mucosa. These criteria also indicate which persons should enter into surveillance programmes. Therefore it is proposed that the rate of referral into surveillance programmes (whether they are part of the screening programme or not) be an essential outcome for evaluating the quality of inspection of colonic mucosa in the context of screening.

It is recommended that screening programmes adopt, as a minimum, the following outcomes to determine the quality of inspection of the colonic mucosa **(VI - A):**[Rec 5.43]

1. Referral into surveillance programmes (see above and Chapter 9); and

2. Withdrawal times from caecum to anus (in patients who have not had biopsy or therapy).

NOTE 1: Monitoring more than one outcome will support quality improvement. For example monitoring withdrawal times might indicate that an individual with low adenoma detection rates may need to withdraw more slowly. However, if acceptable withdrawal times are associated with poor detection rates another solution may be required.

NOTE 2: Different patient populations will have different prevalence rates of neoplastic lesions, thus the standards for different populations will differ.

NOTE 3: To permit monitoring of professional performance, the above minimum outcomes should be generated from complete, individual data sets recorded according to standardised procedures specified by programme rules.

Excision and retrieval of pathological material

Incomplete excision of a high-risk lesion is associated with an increase risk of development of cancer (Winawer et al. 1993). Incomplete removal of tissue may lead to misclassification of pathology (see Chapter 8). There are currently no validated methods of determining completeness of excision but it is possible to measure retrieval rates for pathological material. Chromoendoscopy may facilitate assessment of completeness of excision (see section 5.4.3). At this stage it is recommended that there be raised awareness of the importance of complete excision (or at the very least careful documentation of whether a lesion has been completely excised) and retrieval rates of excised tissue should be recorded.

Information provided for the pathologist

The quality of histopathology is affected by the information provided by the endoscopist and the extent to which the endoscopist and pathologist communicate with each other (see Chapter 7).

Information on histology request forms for suspicious colonic lesions should include (see also Chapter 7):

- Site of lesion;

- Size of the lesion (as estimated by the endoscopist);

- Nature of lesion, including whether it is ulcerated; and

- Completeness of excision as judged by the endoscopist

NOTE: An optimal colonoscopy report will contain this information and it is recommended that a copy of the report should be sent with the pathology request form.

5.4.5.2 Safety outcomes

Adverse outcomes can occur immediately or several days after the procedure. In this context an immediate adverse outcome is defined by an adverse outcome occurring before the patient leaves the endoscopy department. An adverse outcome occurring after this is a late outcome. Endoscopic services must have processes in place to identify and record adverse outcomes occurring after the patient leaves the endoscopy department **(VI - B).**[Rec 5.45]

Three methods are recommended:

- Contacting all patients within a defined time frame;

- 30-day mortality review of all screened patients; and

- 8-day unplanned admission review of all screened patients

It is appreciated that for some health care systems capturing 30-day mortality and 8-day readmissions may be challenging. Furthermore, it is clear that a person may be admitted or die for reasons that have nothing to do with the procedure. The key point is that if there are factors related to the procedure contributing to death or admission, they should be reviewed and an action plan created if the review indicates there is a need for a change in practice.

To simplify the collection of immediate adverse outcomes, it is recommended that unplanned admission on the same day as the endoscopic procedure be a key adverse outcome. It is recommended that the reason for the admission be recorded in the following categories. Furthermore, the primary reason for admission should be indicated **(III - A):**[Rec 5.44]

- Abdominal pain;

- Suspected or confirmed perforation;

- Bleeding;

- Cardio-respiratory event; or

- Other (specify).

5.5   After the procedure

5.5.1   Recovery facilities and procedures

A person having an endoscopy needs a period of recovery, particularly if they have received sedation. There should be a designated area for recovery and sufficient equipment for them to recover (such as chairs and trolleys).

Auditable outcomes: Patient feedback on recovery collected when the patient has recovered from sedation

5.5.2   Emergency equipment and protocols

The recovery area should be equipped with adequate resuscitation and monitoring equipment, and there should be policies and procedures in place for monitoring patients and dealing with emergencies **(VI - B).**[Rec 5.15]

Auditable outcomes: Regular audit of resuscitation equipment check

5.5.3   Patient information – post procedure

Ideally patients should be informed about the outcome of their procedure before leaving the endoscopy unit and given written information that supports a verbal explanation, particularly if they have had sedation **(VI - A).**[Rec 5.26] They need to be told (orally and with written information) whether any follow up will be arranged (written or outpatient), by whom and during what timescales. Oral and written information must contain an explanation of what to do in the event there are problems, and patients should be given a contact telephone number (24 hours/day, 7 days/week) in case of a procedure-related complication.

Auditable outcomes: Patient feedback on adequacy and helpfulness of post-procedure information

5.5.4   Patient feedback

It is essential to obtain patient feedback on a regular basis in order to correct issues that concern patients that health professionals are unaware of. This feedback can be expected to contain considerable

praise for the service provided, and such positive feedback will have a strong motivating effect on staff to provide an even better service.

5.5.5 Communication to other health professionals

The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of their core patient record (see Ch. 2, Sect. 2.4.3.4.2; Ch. 10, Rec.10.31) **(II - B).**[Rec 5.27] In some EU countries the consent of the patient is needed for transmitting the information to the primary care doctor. There should be pre-defined clinical pathways for patients found to require further intervention for cancer, incompletely removed lesions and difficult-to-remove lesions (and failsafe mechanisms to ensure that interventions do occur) **(II - B).**[Rec 5.28]

Auditable outcomes: Time to definitive treatment for patients with cancer; turnaround times for communicating pathology results to patients

5.5.6 Immediate and late safety outcomes

There should be a process in place for systematically recording immediate and late outcomes following screening colonoscopy. See above for types of outcomes and methods of assessment.

Auditable outcomes: Outcomes identified by this process

5.6 Guidelines

The endoscopy service should create and regularly review guidelines for the following, taking into account previous experience and results as well as relevant national and pan-European guidelines containing accepted, published recommendations and standards **(VI - B):**[Rec 5.50]

- Sedation;
- Monitoring after the use of conscious sedation;
- Antibiotic prophylaxis;
- Anticoagulants;
- Colonic cleansing;
- Endoscopic assessment of colorectal abnormalities;
- Endoscopic removal of lesions (both high- and low-risk);
- Marking of high-risk lesions;
- Further management of high-risk lesions; and
- Equipment.

5.7   Policies and processes

There should be policies, and processes to support them, for the following:

• Consent and patient information;

• Withdrawal of consent;

• Decontamination;

• Assessment of competence;

• Staff training;

• Transfer of care following complications;

• Completing the audit cycle; and

• Selection and assessment of equipment.

5.8   References

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[Electronic link to Appendix 1 - Click here*](#)

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

Annex 5.1

Suggested quality indicators and auditable outcomes

Annex 5.1: Suggested quality indicators and auditable outcomes

		QI/AO	mandatory	desirable
1	Age and sex of patient	QI/AO	+	
2	Cancer detection rate (all cancers)	QI/AO	+	
3	Cancer detection rate (endoscopically removed cancers) [1]	QI/AO	+	
4	Referral rate into surveillance programmes (total and by risk category)	QI	+	
5	Adenoma excision and retrieval rate +/- withdrawal times	QI	+	
6.1	Numbers and detection rates of colorectal lesions, in total and broken down by: polypoid and non-polypoid (Paris classification: Ip Ls, IIb IIc sessile non-neoplastic)	QI/AO	+	
6.2	Numbers and rates in 6.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
7.1	Numbers and detection rates of colorectal lesions, in total, and by predicted histology: 1) non-neoplastic (hyperplastic polyp, sessile serrated lesion, other), 2) neoplastic (low-grade adenoma, high-grade adenoma, submucosal carcinoma) and 3) uncommon lesions	QI/AO	+	
7.2	Numbers and rates in 7.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
8.1	Numbers and detection rates of colorectal lesions, in total, and by confirmed histology: 1) non-neoplastic (hyperplastic polyp, sessile serrated lesion, other), 2) neoplastic (low-grade adenoma, high-grade adenoma, submucosal carcinoma) and 3) uncommon lesions	AO	+	
8.2	Numbers and rates in 8.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
9.1	Numbers and rates of discrepant lesions broken down by categories in 7.1 and 8.1	AO	+	
9.2	Numbers and rates of discrepant lesions broken down by categories in 7.2 and 8.2	AO	+	
10	Withdrawal times from caecum to anus (in patients who have not had biopsy or therapy)	QI/AO	+	
11	Colonoscopy completion rate	QI	+	
12	Wait time: FOBT to colonoscopy	QI	+	
13	Wait time: FS to colonoscopy	QI	+	
14	Wait time: colonoscopy to pathology results	QI	+	
15	Wait time: FS to pathology results	QI	+	

16	Wait time: pathology results to definitive treatment	QI	+	
17	Unplanned admission on day of procedure: four options	AO	+	
18	Type of insufflation gas (air or CO_2)	AO	+	
19	Type of sedation used: three options	AO	+	
20	Comfort: only if conscious or no sedation used	AO		+
21	Adequacy of preparation	AO	+	
22	Delayed adverse outcomes: two options	AO	+	
23	Key endoscopic characteristics of polyps written on pathology request form: five key characteristics: number, site, size, completeness of excision, separate pots used for different sites (see also 6–9)	QI	+	
24	Lesions referred elsewhere for excision	AO	+	
25	Patient feedback on information and consent, booking, environment, comfort and aftercare	AO		+
26	Adverse incidents related to incomplete pre-assessment	AO	+	
27	Decontamination indicators	AO	+	

[1] Removed by endoscopic polypectomy and mucosectomy

Annex 5.2

Minimum requirements for endoscopic reporting

Annex 5.2: Minimum requirements for endoscopic reporting

Performance of a unit and staff can be affected by a number of factors.

Therefore for each endoscopically removed lesion it is important to record:

1. Specification of the procedure in which the lesion has been obtained

    1.1. Patient/client information

    1.2. Type of endoscopy (FS or CS)

    1.3. Team performing procedure (endoscopist(s) and ancillary staff

    1.4. Purpose of procedure

        1.4.1. Primary screening

            1.4.1.1. Initial screening or subsequent screening

            1.4.1.2. Interval to last primary screening procedure, if applicable

            1.4.1.3. Interval to last endoscopic examination if not the same as above

        1.4.2. Assessment of abnormal findings

            1.4.2.1. After positive screening test (indicate if FOBT or FS or other)

            1.4.2.2. After positive symptomatic test (indicate if FOBT or FS or other, e.g. symptoms)

            1.4.2.3. For repeat assessment of abnormal findings

        1.4.3. Surveillance

    1.5. Interval to last endoscopic procedure and type of procedure

2. Preparation, insufflation and sedation

    2.1. Bowel cleansing regimen

    2.2. Insufflation gas (air or CO_2)

    2.3. Type of anesthesia and substances used

    2.4. Kit

3. Caecal intubation

    3.1. End of caecum visualized

        3.1.1. Panoramic image of ileo-caecal valve and end of caecum? (Other imaging confirmation of caecal intubation?)

        3.1.2. Signs of inadequate preparation in caecum?

        3.1.3. Intubation time (time at beginning of procedure, time at visualization of end of caecum)

    3.2. End of caecum not visualized:

        3.2.1. Maximum extent of intubation/inspection of colonal mucosa

        3.2.2. Reasons for incomplete examination

4. End of procedure (withdrawal time from caecum)

5. Number of abnormalities detected:

6. For each abnormality detected:

    6.1. Location

        6.1.1. Distance in cm from ano-rectal junction

        6.1.2. Sector: caecum; ascending, transverse, descending colon; sigmoid; rectum

6.2. Size and morphology:

    6.2.1.   Maximum diameter in millimeters

    6.2.2.   Depth in mm and layer (mucosal/submucosal)

    6.2.3.   Mucous patch

    6.2.4.   Polypoid

    6.2.5.   Non-polypoid (Paris classification): Ip Ls, IIb, IIc sessile

6.3. Prediction of histology (endoscopic diagnosis)

    6.3.1.   Non-neoplastic (hyperplastic polyp, sessile serrated lesion, other)

    6.3.2.   Neoplastic (low-grade adenoma, high-grade adenoma[4], submucosal carcinoma)

    6.3.3.   Uncommon lesions

7. When endoscopic treatment is conducted

7.1. Complications (bleeding, use of coagulation, perforation, other adverse effects)

7.2. For each abnormality endoscopically treated:

    7.2.1.   Technique of resection (polypectomy, mucosectomy)

    7.2.2.   Information provided for the pathologist:

        7.2.2.1. Location (see 5.1)

        7.2.2.2. Size and morphology: (see 5.2)

        7.2.2.3. Completeness of excision as judged by the endoscopist)

        7.2.2.4. Prediction of histology (endoscopic diagnosis, see 5.3)

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[4] Very rare mucosal carcinomas, if diagnosed, are included in "mucosal high grade neoplasia and are treated endoscopic biopsy/excision.

6

Professional requirements and training

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Recommendations[1]

General requirements

6.1 Colorectal cancer screening programmes should be operated by an adequately trained multidisciplinary team (see Ch. 8, Rec. 8.1) **(VI - A).**[Sect 6.2; 8.2]

6.2 Key performance indicators should be developed for the monitoring of a national or regional screening programme **(VI - B).**[Sect 6.2]

Administrative and Clerical Staff

6.3 National or regional colorectal cancer programmes should be run in conjunction with other screening programmes by an experienced administrative team **(VI - B).**[Sect 6.3]

6.4 All administrative and clerical staff in a colorectal screening programme should acquire a basic understanding of colorectal screening and specific courses should be developed for this purpose **(VI - A).**[Sect 6.3]

6.5 Management, communication and project management skills for the administrative staff of a colorectal screening programme should be acquired by means of formal courses **(VI - A).**[Sect 6.3]

Epidemiologist

6.6 A specifically trained epidemiologist should be seconded to a national or regional colorectal cancer screening programme **(VI - B).**[Sect 6.4]

6.7 Training of epidemiologists inexperienced in evaluation and monitoring in colorectal cancer screening should be organised as secondments to established screening centres running population-based screening programmes. Additional didactic courses on relevant aspects of the work should be attended depending on individual knowledge and experience **(VI - B).**[Sect 6.4]

Laboratory staff

6.8 A fully trained laboratory staff with appropriate management should be in place for a national or regional colorectal cancer screening programme and internal quality control and external quality assurance mechanisms should be put in place for the laboratory (see Ch. 4, Rec. 4.10 and 4.12) **(VI - A).**[Sect 6.5; 4.3.3.4; 4.3.4]

6.9 Training in the form of courses or secondments to existing laboratories should be available for all laboratory personnel **(VI - B).**[Sect 6.5]

6.10 A European laboratory network should be established in order to provide appropriate external quality assurance **(VI - C).**[Sect 6.5]

Primary care physicians

6.11 All general practitioners should be informed about national or regional colorectal cancer screening programmes and provided with appropriate infrastructure and training, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 2, Rec. 2.12; and Ch. 10, Rec. 10.21) **(II - C).**[Sect 6.6; 2.4.3.4.2; 10.4.2.3.2]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

Endoscopists

6.12 Endoscopists who participate in a colorectal cancer screening programme should be fully trained in colonoscopy or flexible sigmoidoscopy, depending on the procedure they perform in the programme **(V - A).**^{Sect 6.7}

6.13 Endoscopists who participate in a colorectal cancer screening programme should be fully trained in biopsy and polypectomy **(V - A).**^{Sect 6.7}

6.14 Endoscopists who intend to participate in a colorectal cancer screening programme should undergo assessment to ensure an adequate level of expertise before commencing practice within the programme **(VI - B).**^{Sect 6.7}

6.15 Endoscopists who participate in a colorectal cancer screening programme should be able to demonstrate high completion rates, low morbidity and appropriate adenoma detection rates **(VI - B).**^{Sect 6.7}

Radiologists

6.16 Radiologists participating in a colorectal cancer screening programme should have specialist training in colorectal imaging **(VI - A).**^{Sect 6.8}

6.17 Radiologists working within a screening programme should participate in quality assurance where at least a proportion of radiological examinations are double-read **(VI - B).**^{Sect 6.8}

Pathologists

6.18 Pathologists participating in a colorectal cancer screening programme should have specific training in colorectal pathology **(VI - B).**^{Sect 6.9}

6.19 Pathologists participating in a colorectal cancer screening programme should develop a network with other pathologists in order to share experience (see also Ch. 7, Rec. 7.16) **(VI - B).**^{Sect 6.9; 7.6; 7.7}

Surgeons

6.20 Surgeons treating patients with screen-detected disease should specialise (although not necessarily exclusively) in colorectal cancer surgery and should be able to demonstrate a high-volume practice **(III - B).**^{Sect 6.10}

Nurses

6.21 Nurses participating in colorectal cancer screening programmes should have a specific training to equip them with the necessary skills, including adequate training to be able to help people make informed decisions about CRC screening (see Ch.10, Rec. 10.21) **(VI - C).**^{Sect 6.11; 10.4.2.3.2}

Public Health

6.22 Public health physicians should be involved in national or regional colorectal cancer screening programmes and should be provided with appropriate training **(VI - C).**^{Sect 6.12}

6.23 Where necessary, public health specialists should have access to courses or the ability to visit screening centres to obtain this specific training **(VI - C).**^{Sect 6.12}

6.1   Introduction

The success of a colorectal cancer screening programme is dependant on specially trained individuals committed to implementation, provision and evaluation of a high quality, efficient service. The multidisciplinary team that is responsible for a colorectal screening programme includes

- Administrative and clerical staff;

- Epidemiologists;

- Laboratory staff;

- Primary care physicians;

- Endoscopists;

- Radiologists;

- Pathologists;

- Surgeons;

- Nurses; and

- Public health specialists

All staff involved in the delivery of a colorectal cancer screening programme must have knowledge of the basic principles of colorectal cancer screening. To achieve this it would be appropriate for them to attend a course of instruction at an approved training centre prior to the commencement of the programme. The need for specialist training in screening differs between the different disciplines and is most important for those involved in the delivery of the service and diagnosis, e.g. laboratory staff, endoscopists, radiologists, pathologists and nurses. The surgical treatment of screen-detected cancer and post-operative treatment is not performed differently according to whether a cancer is screen detected or symptomatic, but there are certain considerations for the surgeon to take into account when treating a screen-detected cancer. Oncologists are not mentioned in this document, as, stage for stage, their role in the treatment of screen-detected disease is no different from that in symptomatic disease. High-quality screening performance is based on a multidisciplinary approach, and it is important that appropriate training packages are offered. Updating knowledge as part of continuing medical education should be encouraged.

Participation in training courses should be documented and certificates of attendance issued based on the levels of skill attained and evaluated. Specific training requirements in terms of quality and volume should determine eligibility for any certification or accreditation process which must be applied only to centres with sufficiently skilled personnel.

6.2   General requirements

The evidence that Multidisciplinary Teams (MDTs) improve outcomes for cancer patients is still scanty, but beginning to accumulate (Fleissig et al. 2006). However, there is general agreement that multidisciplinary services provide better patient care for a variety of conditions and in colorectal cancer, multidisciplinary management is strongly recommended (NHS Executive 2004). Effective communication between the various professionals of a colorectal multidisciplinary team is essential and training

courses should therefore focus on good inter-professional communication. Joint courses given for the multidisciplinary team may facilitate this goal.

Continuing education including refresher courses at various intervals is essential to gaining information on new developments and to improve the quality of the screening and diagnostic therapeutic processes. It is important to keep records of training activities as they are useful indices of the quality of a service. These would be part of a certification or accreditation review process.

Staff – all staff involved in the screening programme require basic knowledge of the foundation of the programme. Relevant topics are:

- Colorectal cancer epidemiology (incidence, prognosis, mortality);

- Introduction to screening theory;

- Screening terminology (sensitivity, specificity, predictive value, etc);

- Current screening practices (screening modalities used, methods of identifying target population, methods of invitation)

- Evaluation of screening effectiveness (key performance indicators)

Key performance indicators are essential for the effective monitoring of a national or regional colorectal cancer screening programme (Steele et al. 2009). As a bare minimum, the key performance indicators of a colorectal screening programme include:

- Uptake of screening test;

- Time between screening test and definitive diagnosis (where screening test is not colonoscopy);

- Proportion of those with a positive test undergoing colonoscopy (where colonoscopy is not the screening test);

- Colonoscopy completion rate;

- Colonoscopy complication rate;

- Positivity rate (for a non-endoscopic screening test);

- Cancer detection rate;

- Stage of cancer at diagnosis;

- Adenoma detection rate;

- Positive predictive value for cancer and adenomas; and

- Interval cancer rate.

Summary of evidence

- Optimal care is best provided by multidisciplinary teams **(VI).**

- Key performance indicators are essential for effective monitoring of a national or regional screening programme **(VI).**

Recommendations

Colorectal cancer screening programmes should be operated by an adequately trained multidisciplinary team (see Ch. 8, Rec. 8.1) **(VI - A).**[Rec 6.1]

Key performance indicators should be developed for the monitoring of a national or regional screening programme **(VI - B).**[Rec 6.2]

6.3   Administrative and clerical staff

A colorectal screening programme can be run under the umbrella of a screening programmes division associated with the national or regional health department where this exists. This allows the colorectal screening programme staff to benefit from the experience gained from other screening programmes. In the UK, the organisation of the colorectal screening programmes is overseen by a programme manager who reports to a national or regional screening coordinator responsible for all screening programmes. In addition to a programme manager each centre that is responsible for sending out invitations and/or organising screening tests for those who accept the invitations is overseen by a screening manager who is responsible for the efficient operation of the screening programme and managing the staff of the screening centre (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). The staffing of the screening centre depends on the structure of the programme itself; e.g. if it is a centralised programme, staff are required for identifying individuals to be invited, sending out invitations, replying to those who have undergone testing and, where appropriate, organising further investigations for those with positive tests. The basic training requirements for all screening administrative and clerical staff should include the following:

- Basic understanding of colorectal cancer, the potential benefits and harms of screening, and the prime importance of quality assurance
- Basic understanding of the colorectal cancer screening programme; and
- Basic information technology skills.

In addition, the centre manager requires:

- Advanced managerial skills; and
- Advanced communication skills (for dealing with queries, complaints etc).

In addition, the programme manager requires

- Advanced project management skills.

Management communication and project management skills can be acquired by means of formal courses. However the administrative structure required for a colorectal cancer screening programme will depend very much on local and national conditions and must be modified accordingly.

Summary of evidence

- No literature evidence was retrieved for this topic. National and regional screening programmes require an efficient administrative structure **(VI).**

Recommendations

National or regional colorectal cancer programmes should be run in conjunction with other screening programmes by an experienced administrative team **(VI - B).**[Rec 6.3]

All administrative and clerical staff in a colorectal screening programme should acquire a basic understanding of colorectal screening and specific courses should be developed for this purpose **(VI - A).**[Rec 6.4]

Management, communication and project management skills for the administrative staff of a colorectal screening programme should be acquired by means of formal courses **(VI - A).**[Rec 6.5]

6.4   Epidemiologist

As many disciplines contribute to providing data required for monitoring and evaluating a colorectal screening programme it is essential that a designated individual with relevant epidemiological expertise be assigned the task of overseeing the collection and analysis of the data required for evaluation. Assessing a programme's impact on colorectal cancer mortality is only possible if adequate provision has been made in the planning process for adequate collection and analysis of data (see Chapter 3).

Basic Training: The individual overseeing data collection and analysis requires training in clinical epidemiology and statistics.

Specific training: Training for epidemiologists involved in a colorectal cancer screening programme focuses on:

- Colorectal cancer epidemiology (incidence, prevalence, mortality, trends);

- Screening theory (pre-clinical disease, lead time, selection, length bias);

- Colorectal cancer screening terminology (sensitivity, specificity, positive predictive value etc);

- The colorectal screening programme (organisation, current screening modalities);

- Ethical and confidentiality issues;

- Setting up a colorectal cancer screening programme (identification and an invitation of target population, call-recall system, follow-up system);

- Strategies for data collection and management (use of appropriate databases, individual files, computerised archives, linkage to appropriate registries, classification of screening outcomes, quality control procedures and data collection);

- Statistical analysis and interpretation of results (performance indicators for evaluation, predictors of the impact of screening, assessing screening impact and effectiveness, cost-effectiveness calculations); and

- Presentation of data and report writing.

Acquisition of these skills may require specific courses for the individuals involved.

Summary of evidence

- No literature evidence was retrieved for this topic. Careful data collection and analysis is essential for the effective monitoring of a national and regional colorectal screening programme **(VI)**.

Recommendations

A specifically trained epidemiologist should be seconded to a national or regional colorectal cancer screening programme **(VI - B).**[Rec 6.6]

Training of epidemiologists inexperienced in evaluation and monitoring in colorectal cancer screening should be organised as secondments to established screening centres running population-based screening programmes. Additional didactic courses on relevant aspects of the work should be attended depending on individual knowledge and experience **(VI - B).**[Sect 6.7]

6.5   Laboratory staff

Where a screening programme is based on a laboratory test (in the case of colorectal cancer screening the only currently available laboratory test is faecal occult blood testing), it is self-evident that an adequately staffed laboratory is necessary. It is similarly self-evident that the training and skills required by the laboratory staff are dependent on the type of test (guaiac or immunochemical, qualitative or quantitative). The laboratory staff requires supervision by an appropriately qualified individual with expertise in clinical biochemistry (see Ch. 4, Rec. 4.11), and the day-to-day running of the laboratory must be managed by an appropriately skilled scientific officer. When faecal occult blood testing is being used as the primary test for a colorectal screening programme it is essential that this be done with appropriate internal quality control (IQC) and external quality assurance (EQAS) (see Ch. 4, Rec. 4.10 and 4.12, Sect. 4.3.3.4 and 4.3.4); and this requires centralisation, either on a national or regional basis, of the testing process (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). Delegation to individual practitioners is not appropriate.

The training required for the laboratory staff should include the following:

- A basic understanding of colorectal cancer and the benefits of early diagnosis (a basic understanding of the colorectal cancer screening process);

- Training in good laboratory practice;

- Training in the performance of the faecal occult blood test (the specific training will depend on whether a guaiac or immunochemical test is used and whether it is a qualitative or quantitative test); and

- Training in the use of the IT system used to record results.

In addition, the training required by the Laboratory Manager includes:

- Managerial skills;

- An appreciation of internal quality control and external quality assurance; and

- A thorough understanding of the interactions between the laboratory process and the whole screening programme.

An individual with expertise in clinical biochemistry is ultimately responsible for the operation of the laboratory and requires training in the following:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);

- An in-depth understanding of the colorectal cancer screening process (including screening theory and especially the potential benefits and harms of screening and the prime importance or quality assurance);

- Extensive knowledge of performance characteristics of different types of faecal occult blood test; and

- An in-depth understanding of the technology required to perform the faecal occult blood test.

In some parts of Europe the screening programme may not be based on faecal occult blood testing. Where it is, however, it is essential to ensure a uniformly high standard of testing, and a European laboratory network would facilitate this.

Summary of evidence

- No literature evidence was retrieved for this topic. Appropriately trained Laboratory staff are essential for a FOBT-based colorectal cancer screening programme **(VI).**

- No literature evidence was retrieved for this topic. Internal quality control and external quality assurance are essential to ensure consistency of FOBT reporting **(VI).**

Recommendations

A fully trained laboratory staff with appropriate management should be in place for a national or regional colorectal cancer screening programme and internal quality control and external quality assurance mechanisms should be put in place for the laboratory (see Ch. 4, Rec. 4.10 and 4.12, Sect. 4.3.3.4 and 4.3.4) **(VI - A).**[Rec 6.8]

Training in the form of courses or secondments to existing laboratories should be available for all laboratory personnel **(VI - B).**[Rec 6.9]

A European laboratory network should be established in order to provide appropriate external quality assurance **(VI - C).**[Rec 6.10]

6.6 Primary care physicians

There is ample evidence for the importance of involving primary care physicians in the implementation of colorectal cancer screening programmes (see Ch. 2, Rec. 2.8, 2.12 and 2.13; and Sect. 2.3.1 and 2.4.3). The role of primary care physicians in colorectal cancer screening will vary widely from one European country to another. In some instances the general practitioner (GP) is required to invite the target population, in some instances they are required to encourage their patients to participate in a centrally organised screening programme and in some instances they may not play a direct role in the screening programme but will clearly be required to answer questions on screening posed by their patients. It must be emphasised however, that general practitioners should not be encouraged to perform faecal occult blood tests on an individual basis as it is impossible to ensure adequate quality assurance for the performance of the test.

The training required of general practitioners working in an area where there is an active screening programme should include the following:

- A thorough knowledge of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis;

- An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and

- A thorough knowledge of the organisation of the local screening programme and the role of GPs within the programme.

Whenever a colorectal screening programme is introduced into a region it is essential that all GPs serving the region are informed, and that specific training events for GPs are made available, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 10, Rec. 10.21, and Sect. 10.4.2.3.2).

Summary of evidence

The involvement of primary care physicians (general practitioners) in a screening programme can enhance uptake **(I)** (see Chapter 2).

From evidence derived from two good-quality RCTs, it appears that educational programmes on CRC screening rationale, recommendation, CRC risk etc., towards primary care physicians are effective in improving CRC screening rates (Ferreira et al. 2005; Lane et al. 2008). However, a third RCT did not confirm such results (Walsh et al. 2005) **(II).**

Recommendations

All general practitioners should be informed about national or regional colorectal cancer screening programmes and provided with appropriate infrastructure and training, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 2, Rec. 2.12, Sect. 2.4.3.4.2; Ch.10, Rec. 10.21 and Sect. 10.4.2.3.2) **(II - C).**[Rec 6.11]

6.7 Endoscopists

Endoscopists carrying out either flexible sigmoidoscopy or colonoscopy as the primary screening test, or colonoscopy as the investigation following a positive primary screening test, are central to the delivery of a successful screening programme. It is essential that they be skilled in complete examination of the colonic mucosa and in recognising both cancers and pre-cancerous lesions (i.e. adenomas). It is also essential that they be skilled in biopsy and polypectomy technique such that they can carry out lower gastrointestinal endoscopy safely and effectively. If the endoscopy associated with a colorectal cancer screening programme has an appreciable morbidity or mortality, this has the potential to negate any benefit derived from the programme. Likewise if a high proportion of neoplastic lesions are missed on endoscopy, this will undermine the confidence of the population in the screening programme and has the potential to create a damaging "certificate of health" effect.

In order to ensure that only the highest quality of colonoscopy is delivered by the national screening programme in the United Kingdom, a specific assessment process has been introduced, and all colonoscopists wishing to participate in the programme must complete this successfully. The assessment consists of a test of knowledge and direct observation of procedural skills (Shorthouse 2009) (for level of competency for endoscopists see Ch. 5, Sect. 5.1.2).

Different countries will employ different types of health professionals to undertake endoscopy, including medically qualified gastroenterologists, medically qualified surgeons, nurse endoscopists and, in some instances, endoscopists who have neither a formal medical nor a nursing qualification.

In all cases, however, endoscopists working within a colorectal screening programme should meet national professional requirements for performing endoscopy (FS and/or colonoscopy depending on the type of programme and the role of the respective endoscopist) and should fulfil the following training requirements:

- Good knowledge of the normal large bowel, its anatomy and its physiology;

- Good knowledge of the disease processes that can affect the large bowel and its endoscopic appearance;

- An understanding of digital endoscopy technology including maintenance and cleaning;

- Full training in the performance of either flexible sigmoidoscopy or colonoscopy as required including appropriate accreditation where this is available;

- Full training in safe biopsy and polypectomy technique (note: in some instances where endoscopic mucosal resection or endoscopic sub-mucosal resection of extensive lesions is required, tertiary referral may be necessary); and

- Full training in managing complications of endoscopic procedures performed in screening and diagnosis, including local protocols for management of severe complications.

To ensure the requisite high quality of endoscopy within a screening programme, all participating endoscopists must engage in quality assurance, and they must provide the data and reports required to routinely generate returns on numbers of endoscopies performed, completion rates, morbidity rates (including perforation, bleeding and death) and both adenoma and cancer detection rates.

It is difficult to conclude which professional and training requirements for endoscopists can affect the efficacy, safety, tolerability, and accuracy of endoscopic procedures, but evidence suggests that the following patient variables should be identified and taken into account prior to FS or colonoscopy because they can be associated with more adverse events, more time duration, and incomplete examination:

- Use of anticoagulants e.g. warfarin;

- Female anatomy;

- Age of patient;

- ASA (American Society of Anaesthesiologists) physical status;

- Prior abdominal surgery;

- BMI; and

- Diverticular disease.

Furthermore, the conditions under which endoscopy is conducted also have an impact on performance (see Ch. 5, Rec. 5.21, 5.30, 5.37-39, Sect. 5.1.3. 5.3.3 and 5.4.5.1):

- Poor bowel preparation is associated with lower rate of complete colonoscopy;

- Deep sedation is associated with a greater rate of complete colonoscopy but also with a higher risk of cardiovascular events;

- The volume of colonoscopy is associated with completeness of examination and lower complication rates.

Recommendations

Endoscopists who participate in a colorectal cancer screening programme should be fully trained in colonoscopy and/or flexible sigmoidoscopy, depending on the procedure they perform in the programme (Atkin et al. 2004; Thomas-Gibson et al. 2007) **(V - A).**[Rec 6.12]

Endoscopists who participate in a colorectal cancer screening programme should be fully trained in biopsy and polypectomy (Atkin et al. 2004; Thomas-Gibson et al. 2007) **(V - A).**[Rec 6.13]

Endoscopists who intend to participate in a colorectal cancer screening programme should undergo assessment to ensure an adequate level of expertise before commencing practice within the programme(Atkin 2004) However another study did not confirm these results (Aslinia et al. 2006) **(VI - B).**[Rec 6.14]

Endoscopists who participate in a colorectal cancer screening programme should be able to demonstrate high completion rates, low morbidity and appropriate adenoma detection rates **(VI - B).**[Rec 6.15]

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6.8 Radiologists

While the majority of European countries will employ colonoscopy as either the main investigative technique for a positive test or as the primary screening test, radiology expertise is required to investigate the colon in those individuals in whom a complete follow-up or surveillance colonoscopy is not achievable. It is essential that the radiological examination be carried out by an experienced gastrointestinal radiologist. There is evidence that the "miss rate" is highest in situations where a colonoscopy has been incomplete and a subsequent radiological examination has not detected pathology.

Radiologists working within the colorectal cancer screening programme have the following training requirements:

- Good knowledge of the normal colon, its anatomy and physiology;

- Good knowledge of the disease processes that can affect the colon and their radiological appearances;

- An understanding of the technology underlying barium enema and computer tomographic (CT) colography[2]; and

- Full training in the performance of either barium enema or CT colography or both, depending on local availability.

For quality assurance, a proportion of radiological examinations should be double-read. The use of virtual colonoscopy[1] following an incomplete colonoscopy assessment is increasing for patients with poor health. The same requirements, specific for training to barium enema, should apply to virtual colonoscopy.

Summary of evidence

- Currently the role of radiologists in the colorectal cancer screening programme is limited to the investigation of individuals who have undergone incomplete follow-up or surveillance colonoscopies **(V)**.

Recommendations

- Radiologists participating in a colorectal cancer screening programme should have specialist training in colorectal imaging **(VI - A).**[Rec 6.16]

- Radiologists working within a screening programme should participate in quality assurance where at least a proportion of radiological examinations are double-read **(VI - B).**[Rec 6.17]

6.9 Pathologists

Pathologists working within a colorectal cancer screening programme require full training in the histopathology of gastrointestinal disease with specific emphasis on colorectal cancer. These pathologists should be skilled in the following areas:

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[2] CT colography is also known as virtual colonoscopy.

- The interpretation of biopsies taken from benign and malignant tumours of the colon and rectum;
- The preparation and histological interpretation of endoscopic polypectomy specimens; and
- The preparation and histological interpretation of surgical resection specimens.

The histological examination of a polypectomy specimen is a particularly demanding area within a screening programme, as large, complex endoscopically removed lesions are common and often exhibit equivocal features of possible invasive malignancy. It is also particularly important for a pathologist to be able to comment on the degree of differentiation, the presence or absence of lymphovascular invasion, and distance of invasive cancer from the resection margin in endoscopically excised pT1 i.e. "polyp" cancers.

In addition, quality control of surgery is particularly important within a screening programme, as it is essential that individuals with lesions detected at screening are afforded the highest possible standards of care (see Ch. 8). The pathologist has an essential role in the quality assurance of surgery by assessing the completeness of tumour excision in surgical resection specimens.

Pathologists working within a colorectal screening programme have the following training requirements:

- Good knowledge of the disease processes that can affect the colon and their histological appearances;
- An ability to distinguish between benign and malignant biopsy specimens;
- An ability to distinguish between benign and malignant polypectomy specimens;
- An ability to access the risk factors associated with recurrence after endoscopic excision of malignant polyps;
- An appreciation of immunohistochemistry where it relates to histological interpretation of colorectal tumours; and
- The ability to prepare a colorectal resection specimen, with particular emphasis on harvesting lymph nodes and assessing the circumferential resection margin.

Quality assurance in pathology is important and essential within a colorectal screening programme and image exchange is an important component of ensuring consistency of reporting, particularly with the interpretation of difficult endoscopically removed lesions (see Ch. 7, Sect. 7.7).

Summary of evidence

- Colorectal cancer screening results in increased workload for pathology departments, and creates significant demands in terms of the interpretation of complex histology of endoscopically removed lesions (see Ch. 7, Rec. 7.17 and 7.22, Sect. 7.6.5.2) **(V)**.

Recommendations

Pathologists participating in a colorectal cancer screening programme should have specific training in colorectal pathology **(VI – B).**[Rec 6.18]

Pathologists participating in a colorectal cancer screening programme should develop a network with other pathologists in order to share experience (see also Ch. 7, Rec. 7.16, Sect. 7.6 and 7.7) **(VI – B).**[Rec 6.19]

6.10 Surgeons

Most cancers and a small proportion of large adenomas detected within a colorectal screening programme will require surgical excision, and it is important that this be carried out as effectively and safely as possible. The beneficial effect of early detection of colorectal cancer is dependant on low mortality and morbidity rates associated with the subsequent surgery.

It is now recognised that both short- and long-term results of surgery for both rectal and colon cancer are highly surgeon-dependant and there is now good evidence that specialisation associated with high volume is associated with improved results (Morris & Platell 2007; Salz & Sandler 2008). It is therefore mandatory that all screen-detected cancers requiring surgery are treated by surgeons who specialise in colorectal surgery, preferably with a particular interest in cancer. It is also essential that these surgeons work in multidisciplinary teams with access to oncologists experienced in both adjuvant and palliative treatment of colorectal cancer (see Ch. 8, Rec. 8.1).

It follows that surgeons treating patients with screen-detected colorectal cancer should be fully trained and possess the appropriate qualifications for a colorectal surgeon. In addition to the specialist training that this entails, surgeons working within a colorectal screening programme have the following training requirements:

- An understanding of the basic principles of screening, with particular reference to colorectal cancer; and

- An understanding of the significance of pT1 cancers with reference to the need for completion surgery (see Ch. 8, Rec. 8.17).

Screen-detected cancers may be particularly suitable for laparoscopic resection, and it is essential that any surgeon utilising this technique is fully trained and, where appropriate, accredited. While some surgeons may be in a position to obtain appropriate training for laparoscopic surgery within their own institutions, this may not always be the case; and it is essential that surgeons wishing to carry out laparoscopic colorectal surgery should attend the appropriate courses and obtain the appropriate training wherever this is available.

Summary of evidence

- High quality of surgery in a colorectal cancer screening programme is essential to avoid creating unnecessary morbidity in patients requiring surgery for asymptomatic disease. Surgeon specialisation and volume are associated with short- and long-term outcome in colorectal cancer **(III).**

Surgeons

All surgeons treating patients with screen-detected disease should specialise (although not necessarily exclusively) in colorectal cancer surgery and should be able to demonstrate a high-volume practice **(III - B).**[Rec 6.20]

6.11 Nurses

Nurses have important roles throughout the colorectal screening pathway, from the initial contact with the screening invitees through diagnostic endoscopy both as an endoscopy nurse or as a nurse endoscopist, to the care of the patient requiring surgery (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). The importance of these roles will vary from country to country and indeed from region to region within countries. The nursing skills required to care for screening patients are essentially the same as those required to care for symptomatic colorectal patients in many situations. However, the specialist colorectal nurse may have a specific role to play, particularly in counselling individuals with positive screening tests. Such nurses are fully qualified and have experience in specialist colorectal nursing.

The training requirements for nurses in a colorectal cancer screening programme include the following:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis);

- An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and

- Advanced communication skills.

Appropriate courses should be available for nurses involved specifically in colorectal cancer screening programmes to address these issues, including adequate training to be able to help people make informed decisions about CRC screening.

Recommendations

Nurses participating in colorectal cancer screening programmes should have a specific training to equip them with the necessary skills, including adequate training to be able to help people make informed decisions about CRC screening (see Ch.10, Rec. 10.21) **(VI - C).** [Rec 6.21]

6.12 Public health

The role of the public health specialist in a colorectal cancer screening programme is to ensure coordination of the component parts of the screening programme in such a way as to optimise delivery of the programme to the target population (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). This will include endeavouring to maximise uptake by means of health promotion initiatives and addressing inequality issues.

The role of the public health physician may vary from country to country and from region to region within countries, but public health specialists are well placed to act in a coordinating role.

Public health specialists engaging in colorectal cancer have the following training requirements:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);

- An in-depth understanding of the colorectal cancer screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance);

- A full understanding of the mechanisms whereby colorectal cancer screening is delivered in their population; and

- Training in effective health promotion.

Courses or the ability to visit screening centres can provide this specific training.

Summary of evidence

- **No literature evidence was retrieved for this topic.** Public health Physicians have important roles within a Colorectal Cancer Screening Programme in terms of coordination and optimisation of delivery **(VI).**

Recommendations

Public health physicians should be involved in national or regional colorectal cancer screening programmes and should be provided with appropriate training **(VI - C).**[Rec 6.22]

Where necessary, public health specialists should have access to courses or the ability to visit screening centres to obtain this specific training **(VI - C).**[Rec 6.11]

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

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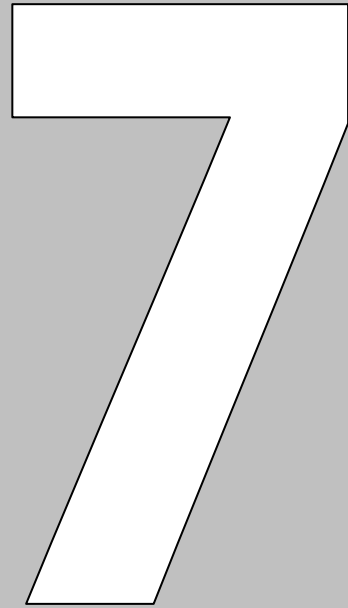
Quality assurance in pathology in colorectal cancer screening and diagnosis

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Recommendations[1]

7.1 Due to the improved diagnostic reproducibility of the revised Vienna classification, use of this classification in a format modified for lesions detected in screening is recommended to ensure consistent international communication and comparison of histopathology of biopsies and resection specimens **(IV – B)**. Only two grades of colorectal neoplasia (low grade and high grade) should be used, to minimise intraobserver and interobserver error **(V - B)**. The terms intra-mucosal adenocarcinoma or *in-situ* carcinoma should not be used **(VI - B)**.[Sect 7.2; 7.3; 7.5.1]

7.2 The WHO definition of colorectal adenocarcinoma should be used: "an invasion of neoplastic cells through the muscularis mucosae into the submucosa" **(VI - A)**.[Sect 7.5.1]

7.3 Adenocarcinomas should be reported according to the TNM classification. The version of TNM to be used should be decided nationally and should be stated e.g. pT1 pN0 pMX (Version 5) or pT4 pN2 pM1 (Version 7). These can be further abbreviated to pT1N0MX **(v5)** or to pT4N2M1 **(v7) (VI - B)**.[Sect 7.6.5.1]

7.4 The WHO classification of adenomas into tubular, tubulo-villous and villous should be used **(VI - A)**.[Sect 7.2]

7.5 Due to the increased risk of colorectal cancer associated with flat and/or depressed lesions they should be reported as non-polypoid lesions **(III)**, and further classified by the Paris classification **(V - B)**.[Sect 7.2; 7.2.3]

7.6 The pathologist should verify the complete removal of neoplastic lesions (clear margins) and the absence of submucosal invasion in biopsy specimens. Currently we recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. Cases of incomplete removal or uncertainty about submucosal invasion should be highlighted in the pathology report **(VI - B)**.[Sect 7.6.3]

7.7 Sub-staging of T1 cancers should be performed to determine the risk of residual disease. Consideration should be given to the appropriate method, which may vary depending on the morphology of the lesion (Kikuchi/Haggitt or measurement). For non-polypoid lesions the Kikuchi stage and for pedunculated lesions Haggitt are currently recommended **(VI - C)**. High-risk features for residual disease such as lack of margin clearance (≤1 mm), poor differentiation and lymphatic and vascular invasion should be reported **(V - B)**. The multidisciplinary team should be consulted on whether or not surgical resection of pT1 adenocarcinoma is recommended; if surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high-risk features **(VI - A)**.[Sect 7.5.3]

7.8 The size of lesions should be carefully measured by the pathologist to the nearest mm on the haematoxylin and eosin slide, or on the fixed specimen when the largest dimension of the lesion cannot be reliably measured on the slide. Endoscopy measurements are less accurate and should only be used when strictly necessary, e.g. if the lesion is fragmented **(III - B)**. Given the small dimensions of the submucosal layer, infiltration into the submucosal level should be measured in microns from the bottom line of the muscularis mucosae **(VI - B)**.[Sect 7.2.1; 7.6.3]

7.9 Programmes should have a policy on the methodology of, and should regularly monitor the accuracy of size measurements of endoscopically removed lesions. Deviation between the actual size and the measurements of pathologists and endoscopists should be minimised. Management decisions which depend on lesion size should take into account potential inaccuracy in the

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

size measurement. The multidisciplinary team should consider deviating from the recommended size categories in treatment and surveillance algorithms, if the review of a case indicates that there is sufficient reason to doubt the accuracy of the measurement. Such cases should be captured as an auditable outcome **(VI – B)**.[Sect 7.2.1]

7.10   Hyperplastic polyps are non-neoplastic and their complete removal is optional. All other lesions in the serrated pathway should be excised and serrated lesions with neoplasia should be followed up (surveillance) as if they were adenomas **(VI- C)**.[Sect 7.1; 7.2.4.4-5]

7.11   All biopsies and lesions identified in the screening programme and the subsequent resection specimen should be reported on a proforma **(IV - B)** in a timely manner and in a minimum of 90% of all cases. The proforma should be sent to the referring physician, the relevant cancer registry and the screening programme **(VI - B)**.[Sect 7.6.5.2; 7.8]

7.12   Dissection of all specimens should be according to national guidelines. If national guidelines do not exist they should be created or adopted from elsewhere. An additional free text written report is optional, but must include all of the data required in the proforma **(VI - B)**.[Sect 7.6.5.2]

7.13   The correlation between histological diagnosis of biopsy and surgical specimens should be reported. Any lack of correlation should be discussed by the multi-disciplinary team, and the results of this discussion should be documented **(III - B)**.[Sect 7.8]

7.14   Pathologists must ensure that their proformas are received by the screening programme coordinators or a cancer registry for the purposes of clinical management, audit and quality assurance. Results from the key indicators of quality should be returned to the funding body: either the Health Authority or the national screening programmes' offices for analysis **(VI - B)**.[Sect 7.8]

7.15   Statistics should include the frequency of colorectal cancer and the distribution of TNM stages and version used, as well as the distribution of the type of lesion, size, location, frequency of grades of neoplasia and villousness (villous, tubulo-villous or tubular) and presence of non-neoplastic lesions **(VI - B)**.[Sect 7.8; 7.5.3.6]

7.16   There should be good communication between the members of the screening team with agreed terminology, regular meetings and clinical discussions **(VI - B)**.[Sect 7.7]

7.17   Pathologists taking part in a colorectal cancer screening programme must participate regularly in multi-disciplinary team meetings, and twice a year in an external quality assurance programme that has external oversight of the results **(VI - B)**.[Sect 7.6; 7.7]

7.18   Departments and individual pathologists should audit their own reporting practices for key features **(VI - B)**.[Sect 7.7]

7.19   Pathologists reporting in a colorectal cancer screening programme must meet their national criteria for safety in reporting colorectal cancer **(VI - B)**.[Sect 7.7]

7.20   Departments and pathologists taking part in screening programmes should audit the number of lymph nodes retrieved, the frequency of circumferential resection margin involvement and the frequency of high-risk features such as extramural vascular invasion, tumour perforation and peritoneal invasion reported **(VI - B)**.[Sect 7.7]

7.21   Pathologists reporting in a colonoscopy screening programme should not report high-grade neoplasia in more than 5% of lesions and those in an FOBT programme in not more than 10% of lesions **(VI - B)**.[Sect 7.7]

7.22   Pathologists should attend one refresher training course every year on the pathology of colorectal neoplasia to maintain quality **(VI - B)**.[Sect 7.6]

7.23   Laboratories participating in a screening programme must be able to demonstrate participation in a laboratory technical external quality assurance programme and hold external accreditation for their services **(VI - C)**.[Sect 7.7]

Further detailed information can be found in the annex to this chapter.

7.1 Introduction

The pathology service plays a very important role in colorectal cancer screening since the management of participants in the programme depends on the quality and accuracy of the diagnosis. Pathology affects the decision to undergo further local and/or a major resection as well as surveillance after screening. The adoption of formal screening programmes leads to improvement not only in the management of early but also advanced disease by the introduction of guidelines, quality standards, external quality assurance and audit. In screening programmes, the performance of individuals and programmes must be assessed and it is advantageous if common diagnostic standards are developed to ensure quality, recognise areas where sufficient evidence is still lacking, and initiate high-quality studies to answer these questions. The present chapter suggests practical guidelines for pathology within a colorectal screening programme. We have concentrated on the areas of clinical importance in the hope of standardising these across the European Union. In the associated annex we deal with some of the more difficult areas and suggest topics for future research. We have included guidelines for the reporting and management of resected specimens in an attempt to move towards agreed minimum European standards of pathology in these areas as well. This is the first edition of what will be a continuing process of revision as new data emerge on the pathology, screening and management of colorectal cancer. We hope to set minimum standards that will be followed in all programmes and to encourage the development of higher standards amongst the pathology community and screening programmes.

Many lesions are found within a screening programme some of which are of little or no relevance to the aim of lowering the burden of colorectal cancer in the population. The range of pathology differs between the different approaches, with faecal occult blood programmes yielding later, more advanced disease than flexible sigmoidoscopy and colonoscopy screening. Programme activities must focus on the identification and appropriate management of invasive colorectal cancer and its precursors. The management of pre-invasive lesions involves surveillance to allow the prevention of future disease, whereas management of adenocarcinoma focuses on immediate treatment and decisions on local removal, or radical surgery with the potential for operative mortality. Overuse of radical surgery must be avoided and recommendations for its use must be balanced with the risks to the patient.

There are a number of lesions, especially in the serrated pathway leading from hyperplastic polyps to other serrated lesions and in some cases to adenocarcinoma, that may be difficult to diagnose and for which knowledge of their natural history and clinical implications is limited (Snover et al. 2005). Further work is required in this area, but until we understand these lesions better it is recommended that all serrated lesions, with the exception of hyperplastic polyps, be fully removed **(V - B).**[Rec 7.10]

Few data were present in the literature on this issue. This paucity of data is caused in part by a lack of standardisation in terminology and limited observer agreement. Furthermore, a lack of prospective studies precludes a clear indication of the optimal treatment and surveillance strategy for lesions in the serrated pathway. For more information, see the annex to this chapter. The screening programme will also identify other non-serrated neoplastic and non-neoplastic lesions and provide important data on such conditions.

7.2 Classification of lesions in the adenoma-carcinoma sequence

A colorectal adenoma is defined as a lesion in the colon or rectum containing unequivocal epithelial neoplasia. Classification of adenomas should include grading of neoplasia according to the revised Vienna classification that has been modified for the European Guidelines to obtain a two-tiered system of low-grade and high-grade neoplasia (Table 7.1); see also Kudo et al. (2008). This modified grading system aims to minimise intra- and inter-observer variation and facilitate management of endoscopically detected lesions by improving correlation between histopathology of biopsies and resection specimens (Tominaga et al. 2009). Classically, adenomas are divided into tubular, tubulo-villous or villous types and demarcation between the three is based on the relative proportions of tubular and villous components, according to the "20% rule" described in the WHO classification of tumours in the digestive tract (WHO 2000). At least 20% of the estimated volume of an adenoma should be villous to be classified as a tubulo-villous adenoma and 80% villous to be defined as a villous adenoma. All other lesions are classified as tubular (WHO 2000) **(VI - A).**[Rec 7.4] The reproducibility of villousness increases when collapsing the categories into only two: tubular vs. any villous component (i.e. anything >20% villous). Adenomas can be endoscopically polypoid, flat or depressed. Due to the increased risk of colorectal cancer associated with flat and/or depressed lesions **(III)** they should be reported as non-polypoid lesions (see Sect. 7.2.3). The Paris endoscopic classification of superficial neoplastic lesions should be used to describe the gross appearance of colorectal adenomas **(V - B).**[Rec 7.5] Key features to report in a programme are size, villousness, the grading of neoplasia, the recognition of invasion and features suggesting the need for further intervention either local or radical. The size of adenomas is important for their risk of containing an adenocarcinoma but it is also related to the need for subsequent surveillance, or colonoscopy.

The two-tiered grading of mucosal colorectal neoplasia recommended in the European Guidelines (see Table 7.1) is based on the revised Vienna Classification that has improved diagnostic reproducibility, particularly for non-polypoid lesions (Schlemper et al. 2000; Schlemper, Kato & Stolte 2001; Dixon 2002; Stolte 2003; Suzuki et al. 2006) **(IV - B).**[Rec 7.1] The recommended two-tiered grading system also permits translation of histopathology findings of Western and Japanese pathologists into a uniform system for classification of colorectal neoplastic lesions.

In screening programmes the use of the term advanced adenoma has developed and is sometimes used to categorise adenomas for management. In this context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component.

The hyperplastic polyp must be distinguished from other serrated lesions due to its extremely low malignant potential. The significance of other lesions in the serrated spectrum is controversial and our knowledge is still developing; traditional serrated adenomas and mixed polyps with neoplasia should be considered as adenomas for the purpose of follow-up (surveillance). More details are provided in the annex.

7.2.1 Measurement of size of adenomas

Size (largest diameter) is an important objective measurement best performed by the pathologist (Schoen, Gerber & Margulies 1997) from the slide, as is recommended in the EU Guidelines for breast cancer screening (EC Working Group on Breast Screening Pathology 2006). Endoscopy measurements are less accurate and should only be used when strictly necessary **(III - B).**[Rec 7.8] Pathology meas-

urements are auditable, accurate, simple to perform and able to assess the size of the adenomatous component of mixed lesions. Although the quality of evidence is low, there are some indications that different modalities of advanced adenoma measurement (endoscopic measurement vs. pathologist's measurement before and after fixation, slide preparation) can affect diagnostic reproducibility and the detection rate of advanced adenomas. An overestimation or underestimation of a large or a small polyp is important when the misjudgement crosses the 10 mm threshold. It seems that the use of the pathologist's measurement is currently the most accurate. If the lesion is too large for the maximum dimension to be measured by this method, because it cannot be represented on a single slide, the measurements taken at the time of specimen dissection should be used. If a biopsy is received or the specimen is fragmented it should be stated that it cannot be accurately assessed for size by the pathologist and the endoscopy measurements should be used. Measurements should exclude the stalk if it is composed of normal mucosa however the distance to the excision margin should be noted. The size of adenomas is used to determine the need for surveillance and therefore must be measured accurately to the nearest millimetre (and not rounded-up to the nearest 5 or 10 mm). Where the lesion is mixed or only part of a lesion is adenomatous, measurement should be performed on the adenomatous component.

Programmes should have a policy on the methodology of, and should regularly monitor the accuracy of size measurements of endoscopically removed lesions. Deviation between the actual size and the measurements of pathologists and endoscopists should be minimised. Management decisions that depend on lesion size should take into account potential inaccuracy in the size measurement. The multidisciplinary team should consider deviating from the recommended size categories in treatment and surveillance algorithms, if the review of a case indicates that there is sufficient reason to doubt the accuracy of the measurement. Such cases should be captured as an auditable outcome **(VI - B).**[Rec 7.9]

7.2.2 Tubular, tubulo-villous and villous adenomas: the typing of villousness

The 20% rule only applies to wholly excised polyps and to intact sections of lesions large enough to provide reliable proportions. For small fragmented lesions or superficial polyp biopsies, the presence of at least one clearly identifiable villus merits classification as "at least tubulo-villous". Definitions of the types of villousness are presented in the annex.

7.2.3 Non-polypoid adenomas

The role of the pathologist in the evaluation of non-polypoid adenomas is to confirm the adenomatous nature of the lesion, and to determine the grade of neoplasia as well as the depth of depression in the case of a depressed non-polypoid lesion (see below). Since the expression "flat adenoma" is not well defined it is recommended to group together all adenomatous lesions other than polypoid into the category of "non-polypoid adenomas" and avoid the term "flat". Non-polypoid adenomas correspond to an endoscopical diagnosis of neoplasia in the subtypes IIa, IIb and IIc according to the Paris classification. Completely flat adenomas (type IIb) and depressed lesions (type IIc) are rarely found in the colon and rectum, while slightly elevated lesions (type IIa) are frequent. In the literature, the height of non-polypoid adenomas has been described histologically as not exceeding twice the height of normal mucosa, thus measuring less than 3 mm in height. This definition may be difficult to apply due to fixation artefacts and in slightly depressed lesions since the adjacent mucosa may be thinner than the normal epithelium. The endoscopic diagnosis of a non-polypoid lesion should be reported according to the Paris classification (The Paris Classification 2003; Suzuki et al. 2006; Kudo et al. 2008; Soetikno et al. 2008) **(III - B).**[Rec 7.5] We were unable to retrieve studies that specifically address the

topic of the differences in the detection rates of non-polypoid colorectal neoplasms among the different types of screening programmes (FOBT vs. FS vs. TC), although a prevalence of 9–10% of non-polypoid colorectal neoplasm (flat and depressed) was recently reported by Western pathologists in a large cross-sectional study (Soetikno et al. 2008). Depressed lesions (type IIc) should be mentioned in the histological report for clinico-pathological correlation. Special care should be taken for centrally depressed lesions, especially when the depression is deeper than half of the adjacent lesion. These are reported to have a higher frequency of high-grade neoplasia and invasion at a smaller size than other flat or depressed lesions (Kudo et al. 2008). Non-polypoid adenomas can show so-called lateral spread with poor delineation of the margins thus making endoscopic removal difficult.

7.2.4   Serrated lesions

7.2.4.1   Terminology

These lesions have in common a serrated morphology, but depending on other characteristics, the potential to develop into invasive adenocarcinoma differs considerably. Serrated lesions vary from the *hyperplastic polyp*, which although relatively common, has no implications for the screening programme unless very numerous, proximally located or of a large size (>10 mm), to *sessile serrated lesions* (sometimes referred to as *sessile serrated polyps/sessile serrated adenomas*), *traditional serrated adenomas*, or *mixed lesions/mixed polyps*. Serrated lesions are infrequent, the evidence base is poor and recommendations are not well established, but until further evidence is forthcoming we recommend the following:

7.2.4.2   Hyperplastic (metaplastic) polyp

Hyperplastic polyps (HPs) are often small lesions (<5 mm in diameter), frequently found in the left (distal) colon. They are composed of simple elongated crypts with a serrated structure in the upper half. These polyps usually show some proliferation in the basal (non-serrated) part of the crypts (regular proliferation). Nuclei are small, regular and basally orientated. There is no hyperchromasia, and stratification of the upper half of the crypts has a serrated appearance without cytological atypia.

Hyperplastic polyposis should be excluded in cases with giant hyperplastic polyps (>10 mm), or multiple hyperplastic polyps in the right colon, or in first-degree relatives of individuals with hyperplastic polyposis.

7.2.4.3   Sessile serrated lesions

We recommend the use of the term sessile serrated lesion (SSL) for serrated lesions with structural alterations that do not show mucosal neoplasia. This term should replace the use of sessile serrated polyp and sessile serrated adenomas until better definitions are created.[2] It is not recommended to use the latter terms in screening programmes because it would add additional ill-defined categories that may confuse practitioners.

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[2] The term *sessile serrated polyp* has been proposed elsewhere for serrated lesions that cannot be definitely classified into the category of *hyperplastic polyps* or *serrated adenomas* (Snover et al. 2005), especially in cases with technical inconsistencies such as tangential cuts or superficial biopsies. The same terminology has been propsed for lesions with minimal and focal structural alterations in the absence of cytological atypia (Torlakovic et al. 2008).

7.2.4.4 Traditional serrated adenomas

If the lesion shows a serrated morphology as well as mucosal neoplasia (cytological abnormalities), it is considered to be a traditional serrated adenoma (TSA) (Longacre & Fenoglio-Preiser 1990). It should be reported as such (TSA) and treatment and surveillance should be the same as for adenomas. See annex and Chapter 9 for details. This pragmatic recommendation recognises the neoplastic nature of these lesions. The non-serrated features found in such lesions (e.g. size and grade of neoplasia) and any co-existing pathology (e.g. number of neoplastic lesions) should be taken into account in selecting an appropriate surveillance protocol **(VI - C).**[Rec 7.10]

7.2.4.5 Mixed polyp

These are lesions with combinations of more than one histopathologic type in the serrated spectrum (hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas) or at least one type in combination with adenoma (Jass et al. 2006). The important feature to recognise for the screening programme is the presence of neoplasia. The respective types of lesion in a mixed polyp should be reported and the term "mixed polyp" should only be used in brackets after the diagnosis of the individual components (e.g. adenoma and hyperplastic polyp, or traditional serrated adenoma plus adenoma). Mixed polyps should be completely removed. If there is an adenomatous component, the lesion should be followed up (surveillance) in the same manner as for adenomas, taking into account the size and the grade of the adenomatous component. **(VI - C).**[Rec 7.10]

7.3 Grading of neoplasia

The revised Vienna classification has been adopted here, but in a simplified form suitable for screening and diagnosis, by removing the indefinite category between "negative for neoplasia" and "low-grade neoplasia". This category has no clinical value and unlike inflammatory bowel disease is likely to be chosen very infrequently. Excluding it reduces the number of categories and simplifies the subsequent management choices. The advantages of the revised Vienna Classification on which the European screening classification is based are that it improves diagnostic reproducibility (Schlemper et al. 2000; Dixon 2002; Stolte 2003; Suzuki et al. 2006) **(IV - B).** The modified format with a two-tiered grading of mucosal colorectal neoplasia aims to further reduce inter-observer variation (Fenger et al. 1990) **(V - B).**[Rec 7.1] It encompasses the diagnostic categories used in the Eastern and the Western schools and each level has a clinical consequence. In the revised Vienna classification the term neoplasia is used which is synonymous with the formerly used term "dysplasia". In the two-tiered grading system recommended in the European Guidelines, mucosal low-grade neoplasia corresponds to neoplasia of the same grade in the revised Vienna classification; mucosal high-grade neoplasia likewise corresponds to neoplasia of the same grade in the revised Vienna classification. Invasive submucosal neoplasia in the European classification corresponds to carcinoma invading the submucosa or beyond in the Vienna classification (see Table 7.1).

7.3.1 Low-grade neoplasia

Low-grade neoplasia is an unequivocal neoplastic condition confined to the epithelial glands. It should not be mistaken for inflammatory or regenerative changes. Alterations characteristic for low-grade

neoplasia start from one gland and develop into a microadenoma that then grows to become macro-scopically visible. Caution should be exercised in patients with chronic inflammatory bowel disease where the diagnosis of a neoplastic sporadic adenoma has implications different from that of neoplasia in colitic mucosa.

7.3.2 High-grade neoplasia

The changes of high-grade neoplasia should involve more than just one or two glands (except in tiny biopsies of polyps), and should therefore be identifiable at low-power examination. Caution should be exercised in over-interpreting isolated surface changes that may be due to trauma, erosion or prolapse.

Table 7.1: Adaptation of the revised Vienna classification[1] for colorectal cancer screening

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1. NO NEOPLASIA:[2]
    Vienna Category 1 (Negative for neoplasia)

2. MUCOSAL LOW GRADE NEOPLASIA:
    Vienna Category 3 (Mucosal low-grade neoplasia
        Low-grade adenoma
        Low-grade dysplasia);
    Other common terminology
        mild and moderate dysplasia;
    WHO: low-grade intra-epithelial neoplasia

3. MUCOSAL HIGH GRADE NEOPLASIA:
    Vienna: Category 4.1–4.4 (Mucosal high grade neoplasia
        High-grade adenoma/dysplasia
        Non-invasive carcinoma (carcinoma *in situ*)
        Suspicious for invasive carcinoma
        Intramucosal carcinoma);
    Other common terminology
        severe dysplasia;
        high-grade intraepithelial neoplasia;
        WHO: high-grade intraepithelial neoplasia
        TNM: pTis

4. CARCINOMA invading the submucosa or beyond:
    4a. Carcinoma confined to submucosa
        Vienna: Category 5 (Submucosal invasion by carcinoma);
        TNM: pT1
    4b. Carcinoma beyond submucosa
        TNM: pT2-T4

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[1] For revised Vienna classification see Dixon (2002), for WHO classification see WHO (2000), for TNM see (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009).

[2] Category 2 of the Vienna Classification (indefinite) is not recommended for screening.

High-grade neoplasia is diagnosed on structure, supplemented by an appropriate cytology. Hence its presence is nearly always suspected by the low-power appearances where complex structural abnor-

malities are present in structures whose epithelium looks thick, blue, disorganised and with focal cell debris and necrosis.[3] The structural features are:

- complex glandular crowding and irregularity (note that the word "complex" is important and excludes simple crowding of regular tubules that might result from crushing);

- prominent glandular budding;

- a cribriform appearance and "back to back" glands; and

- prominent intraluminal papillary tufting.

While many of these features often co-exist in high-grade neoplasia, individually they are neither necessary nor usually sufficient. Indeed they may occasionally occur in lower grades of neoplasia and that is why it is necessary to further scrutinise the cytological features for signs of high-grade neoplasia. The cytological features of high-grade neoplasia are:

- loss of cell polarity or nuclear stratification. High-grade neoplasia should show at least 2–5 nuclear rows and preferably a variable number of rows within individual glands. The nuclei are haphazardly distributed within all three thirds of the height of the epithelium. No maturation of the epithelium is seen towards the luminal surface;

- neoplastic goblet cells (retronuclear/dystrophic goblet cells);

- cytology includes vesicular or/and irregular round nuclei with loss of polarity whereas spindle-like palisading nuclei are a sign of low-grade intraepithelial neoplasia;

- markedly enlarged nuclei, often with a dispersed chromatin pattern and a prominent nucleolus;

- atypical mitotic figures; and

- prominent apoptosis, focal cell debris and necrosis.

Again, these features usually coexist in high-grade neoplasia, and caution must be exercised in using just one. It should be emphasised again that they should occur in a background of complex structural abnormality. Marked loss of polarity and nuclear stratification sometimes occurs on the surface of small, structurally regular, tubular adenomas that otherwise have a lower grade of neoplasia, probably as a result of trauma, and must not be used to classify a lesion as high grade. The only exception to the rule is when the specimen consists of just a small biopsy from a polyp, when there is insufficient tissue to assess the architecture properly. In this situation it is permissible to label florid cytological abnormalities alone as high-grade neoplasia, but this will usually lead to re-excision of the whole polyp, when it will be possible to assess the whole lesion properly.

Also included within high-grade neoplasia is the presence of definite invasion into the lamina propria of the mucosa but not invasion through the mucscularis mucosae.

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[3] High-grade neoplasia also contains the subgroup of intramucosal carcinoma used by some pathologists but not recommended here. For details see the annex.

7.4 Other lesions

7.4.1 Inflammatory polyps

Experience from United Kingdom pilot sites has shown that inflammatory-type polyps are relatively common. Whilst they are most usually seen as a complication of chronic inflammatory bowel disease, particularly ulcerative colitis, they are also seen in association with diverticulosis, mucosal prolapse and at the site of ureterosigmoidostomy. Furthermore, sporadic, single inflammatory-type polyps (inflammatory cap polyp, cloacogenic inflammatory polyp, myoglandular polyp, granulation tissue polyp etc.) are well described in the colorectum. As the reporting pathologist may not know the true context of such polyps, we recommend that all such polyps be classified as "post inflammatory polyp". The term inflammatory pseudopolyp (or even just "pseudopolyp") should be avoided. Biopsies with mucosal prolapse syndrome should be identified and reported as such and not as neoplastic conditions.

7.4.2 Juvenile polyps

Juvenile polyps are spherical in shape, show an excess of lamina propria, and have cystically dilated glands. The expanded lamina propria shows oedema and mixed inflammatory cells. Experience from the UK faecal occult blood pilot sites suggests that occasional juvenile-type polyps are identified, even in the screening age group (Jass et al. 1988). Juvenile polyps are most common in children but occasional examples are seen in adults. We advise that any polyp showing juvenile polyp-type features should be classified as "juvenile polyp" for the purposes of diagnostic reporting in a screening programme. Juvenile polyps often show epithelial hyperplasia but neoplasia is very rare. Single sporadic juvenile polyps have a smooth surface, can be found in all age groups and often are eroded. So-called "atypical juvenile polyps" show different morphological features, with a multilobated architecture, intact surface mucosa and (usually) a much more pronounced epithelial component. They are a characteristic feature of juvenile polyposis (JP).

7.4.3 Peutz-Jeghers polyps

Whilst these polyps are usually seen in the Peutz-Jeghers syndrome, occasional examples are demonstrated as single, sporadic polyps in the colon. There remains uncertainty as to whether "inflammatory myoglandular polyp" represents a similar entity. As with juvenile polyposis, it would seem most unlikely, given the rarity of the syndrome and the age of the screening population, that Peutz-Jeghers syndrome would be diagnosed as part of a screening programme. Although Peutz-Jeghers polyps are classified as hamartomas, they have a very organised structure. They have a central core of smooth muscle with conspicuous branching, each branch being covered by colorectal-type mucosa that appears hyperplastic but not neoplastic. As with sporadic juvenile polyps, solitary Peutz-Jeghers-type polyps are most unlikely to demonstrate foci of neoplasia.

7.4.4 Serrated (hyperplastic) polyposis

This condition is characterised by one or more of the following conditions (Burt & Jass 2000):

- At least 5 histologically diagnosed serrated polyps proximal to the sigmoid colon, of which 2 are >10 mm;

- Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; and/or

- More than 30 serrated polyps of any size, but distributed throughout the colon.

As mentioned in Section 7.2.4.2, hyperplastic polyposis should be excluded in cases with giant hyperplastic polyps (>10 mm), hyperplastic polyps in the right colon or in first-degree relatives of individuals with hyperplastic polyposis.

7.4.5 Cronkhite-Canada syndrome

We believe it is most unlikely that such cases will present via a screening programme and the true diagnosis may not be recognised by pathological assessment. However if Cronkhite-Canada syndrome is suspected, the pathologist should contact the endoscopist and ask for clinical details to ensure the diagnosis.

7.4.6 Neuroendocrine tumour

It is recommended to use the term "neuroendocrine tumour" rather than carcinoid in accordance with the WHO classification. These lesions are usually benign, small lesions and do not give rise to diagnostic difficulty.

7.4.7 Colorectal intramucosal tumours with epithelial entrapment and surface serration

Entrapment and pseudoinvasion of glands into the submucosal layer must be distinguished from invasive carcinoma. If in doubt, the relevant findings should be stated in the written report. If evaluation is problematic, step sections, a second opinion and further biopsies from the polypectomy ulcer should be considered.

7.4.8 Non epithelial polyps

- Lipoma
- Leiomyoma of the muscularis mucosae
- Ganglioneuroma
- Gastrointestinal schwannoma
- Neurofibroma

- GIST

- Various forms of vascular tumour

- Perineurioma

- Fibroblastic polyp

- Epithelioid nerve sheath tumour

- Inflammatory fibroid polyp

7.5 Assessment of the degree of invasion of pT1 colorectal cancer

pT1 cancers are those showing invasion through the muscularis mucosae into the submucosa but not into the muscularis propria.

7.5.1 Definition of invasion

We recommend the use of the WHO definition (WHO 1989; WHO 2000) of an adenocarcinoma as **an invasion of neoplastic cells through the muscularis mucosae into the submucosa (VI- A).**[Rec 7.2] The term intramucosal carcinoma should be substituted by mucosal high-grade neoplasia according to the WHO classification and the modified classification of neoplasia recommended in the European Guidelines based on the revised Vienna classification (see Table 7.1). We recognise that this will not allow detailed comparison with Japanese series where, contrary to the previous US and European literature, a diagnosis of carcinoma can be made on cases of neoplasia without submucosal invasion, or even on the basis of marked intraepithelial atypia. The TNM classification (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009) allows carcinoma *in situ* (Tis) but this does not improve on the revised Vienna classification and should not be used. Please see annex for details **(VI - D).**[Rec 7.1]

Careful consideration should be given to the potential for surgical overtreatment of misclassified early T1 cancers. Screening programmes require explicit criteria for the diagnosis and staging of early adenocarcinoma because unnecessary radical resection will raise the morbidity and mortality in colorectal cancer screening programmes. Please see annex for further discussion of this point. Post-operative mortality (within 30 days) ranges between 0.6% and 4.4% in T1 cancers depending on the population, age of patient and quality of services available. Achieving the optimum balance between removing all disease by resection and minimising harm is very important.

7.5.2 Epithelial misplacement

Epithelial misplacement of adenomatous epithelium into the submucosa of a polyp is a well-recognised phenomenon (Muto, Bussey & Morson 1973). It is commonly seen in prolapsing polyps in the sigmoid colon. Experience suggests that this will be one of the most difficult areas of pathological diagnostic

practice in FOBT screening. Sigmoid colonic polyps are particularly prone to inflammation, a feature that tends to enhance the neoplastic changes present. When associated with epithelial misplacement, the potential for misdiagnosis of these lesions as early carcinoma become much greater. In cases of epithelial misplacement, surrounding lamina propria and haemosiderin-laden macrophages are found. Sub-mucosal mucinous lakes may be seen. These do not warrant an immediate diagnosis of invasion and must be interpreted in association with the surrounding features.

7.5.3 High risk pT1 adenocarcinoma

pT1 tumours provide many difficulties in a screening programme and the current evidence base for management of these lesions is poor and based on symptomatic patients (Coverlizza et al. 1989; Cooper et al. 1995; Volk et al. 1995; Blumberg et al. 1999; Hassan et al. 2005) **(V - B).**[Rec 7.7] With regard to the correlation between clinical outcomes and tumour pathology, a clear indication of an increased risk of residual disease, lymph-node metastasis, haematogenous metastasis and mortality was observed after endoscopic polypectomy and subsequent surgical resection of poorly differentiated tumours (i.e. tumours with incomplete excision, poor grade of histological differentiation, venous and lymphatic invasion, tumour budding). Some pathology features, such as tumour budding and lymphatic and venous invasion appeared as possible prognostic factors for increased risk of lymph node metastasis but a clear guideline cannot be drawn as this correlation was not statistically significant in all studies. The available methods for sub-staging and differentiation grading are shown below. The most appropriate method depends on the morphology of the lesion and depth of invasion, e.g. non-polypoid – Kikuchi levels, and polypoid - Haggitt levels. In the future more quantitative measurements should be investigated as suggested by the Japanese.

7.5.3.1 Sub-staging pT1

In pT1 tumours the frequency of lymph node metastasis in tumours that involve the superficial, middle and deep thirds of the submucosa, i.e. so-called Kikuchi levels sm1, sm2 and sm3 (Figure 7.1) (Kudo 1993; Kikuchi et al. 1995) has been reported to be 2%, 8% and 23%, respectively (Nascimbeni et al. 2002).

Figure 7.1: Kikuchi levels of submucosal infiltration modified from Nascimbeni et al. (2002)
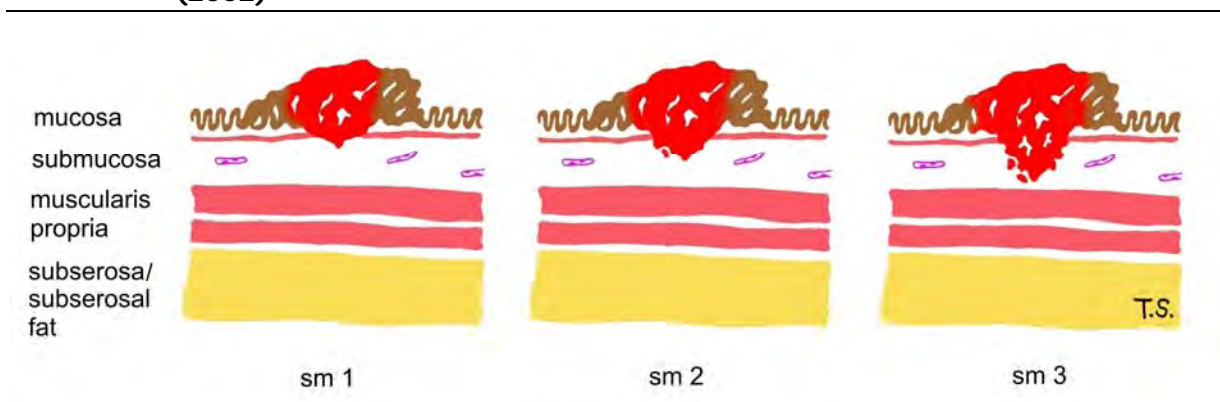
In pedunculated polypoid lesions, Haggitt identified the level of invasion into the stalk of the polyp (Figure 7.2) as being important in predicting outcome and found that level 4 invasion, in which the tumour extended beyond the stalk of the polyp into the submucosa, but did not invade the muscularis propria, was an adverse factor (Haggitt et al. 1985).

However, both the Kikuchi (for non-polypoid tumours) and the Haggitt (for pedunculated tumours) systems may be difficult to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue, and one study found lymph node metastases in 6/24 Haggitt level 3 lesions. More recently Ueno et al. (2004) have proposed use of the depth (>2000 µm) and width (>4000 µm) of invasion measured in microns beyond the muscularis mucosae provides a more objective assessment of lymph node metastatic potential (2.5% vs. 18.2% when submucosal invasion width is < or ≥4000 µm, respectively; and 3.9% vs. 17.1%, when submucosal invasion depth is < or ≥2000 µm, respectively; and this approach has been adopted in Japan. Each classification has advantages and disadvantages.

Figure 7.2: Haggitt levels of invasion in polypoid carcinomas

Level 1:
invasion of the submucosa but limited to the head of the polyp

Level 2:
invasion extending into the neck of polyp

Level 3:
invasion into any part of the stalk

Level 4:
invasion beyond the stalk but above the muscularis propria
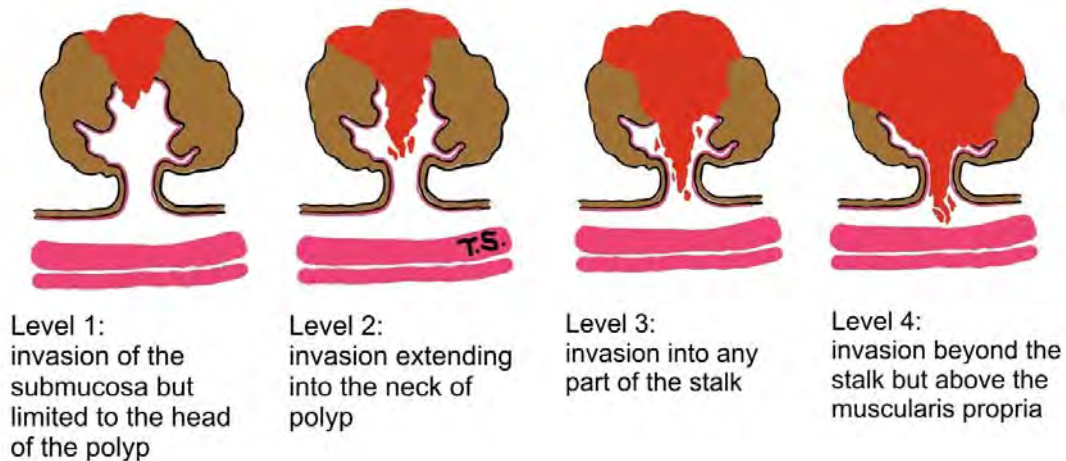
Kikuchi cannot be used in the absence of muscularis propria; Haggitt is not applicable in non-polypoid lesions, and measurement depends on a recognisable submucosa from which to measure. In view of the uncertainty and lack of consensus, a firm evidence-based recommendation for one method of assessing local invasion cannot yet be made. At present we recommend the Kikuchi stage for non-polypoid lesions and Haggitt for pedunculated lesions **(VI - C)**. All three approaches must be evaluated in further large series from multiple programmes to derive adequately evidence-based recommendations.

7.5.3.2   Tumour grade in pT1 lesions

Poorly differentiated carcinomas are identified by the presence of either irregularly folded, distorted and often small tubules or the lack of any tubular formation and showing marked cytological pleomorphism. In the absence of good evidence we recommend that a grade of poor differentiation should be applied in a polyp cancer when ANY area of the lesion is considered to show poor differentiation. Poor differentiation should equate to the WHO categories of poor and undifferentiated tumours (Washington et al. 2009). The frequency should not exceed 20%. According to the WHO classification (WHO 1989), budding of the tumour cells at the front of invasion should not influence grading of the tumour. Please see annex for details.

7.5.3.3   Lymphovascular invasion in pT1 adenocarcinomas

Definite invasion of endothelium-lined vascular spaces in the submucosa is generally regarded as a significant risk for lymph node or distant metastasis. Sometimes retraction artefact around tumour aggregates can make assessment uncertain, in which case this uncertainty should be recorded and the observation should be interpreted in a multidisciplinary conference in the light of any other adverse

histological features. At the moment there are no consistent data available on the additional use of immunohistochemistry, but this might be helpful in distinguishing retraction artefacts from lymphatic (e.g. LEM D 2-40) or capillary spread (e.g. CD 34).

7.5.3.4 Margin involvement in pT1 adenocarcinomas

It is important to record whether the deep (basal) resection margin is involved by invasive tumour (that may be a reason for further surgery) and whether the lateral mucosal resection margin is involved by carcinoma or the pre-existing mucosal neoplasia (in which case a further local excision may be attempted) **(VI - B).**[Rec 7.6]

There has been considerable discussion and controversy in the literature over what degree of clearance might be regarded as acceptable in tumours that extend close to the deep submucosal margin (Cooper et al. 1998). It is important that clearance be measured and recorded in the report. All would agree that a clearance of 0 mm, and most would agree that a clearance of <1 mm is an indication for further therapy, others would use <2 mm. We currently recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. However, this may be handled by removal of any residual polyp endoscopically.

7.5.3.5 Tumour cell budding in pT1 adenocarcinomas

Tumour cell budding, i.e., the presence of small islands or single infiltrating tumour cells at the front of tumour invasion, has been described in the Japanese literature as an unfavourable prognostic factor if present in a marked degree (Sakuragi et al. 2003; Ueno et al. 2004; Masaki et al. 2006). Budding has been assessed either as slight, moderate or marked; or as present/absent (Deinlein et al. 2003; Wang et al. 2005). However, its reproducibility has been criticised, the diagnostic criteria vary (Prall 2007) and the ability to predict metastasis compared to the previously discussed factors is unproven. Further research is needed in this area to identify the optimum method and its reproducibility before tumour cell budding can be recommended for routine use as an indicator of metastasis. Please see annex for details.

7.5.3.6 Site

The site of origin of each specimen should be individually identified by the clinician and provided to the pathologist on the request form **(VI - B).**[Rec 7.15] This should preferably include both the segment of the bowel and the distance in cm from the anus. The pathologist should record this information on the proforma. This is important as the risk of lymph node metastases from a T1 adenocarcinoma has been reported to vary depending on the site of the lesion (Okuyama, Oya & Ishikawa 2002).

7.6 Specimen handling

Specimen handling is an important issue, as poor handling and dissection procedures can impair diagnostic accuracy. Specimen handling starts with the endoscopic removal of the specimen and ends with the histopathological diagnosis and report. The need for a close relationship between endoscopists and histopathologists is stressed.

7.6.1   Submission of specimens

It is recommended to place specimens in separate containers, one for each lesion, to avoid confusion about exact location; if lesions are small, individual cassettes or multicassettes can be used. Biopsies from the same lesion can be placed in the same container. For endoscopic resections it is helpful to pin out specimens by inserting pins through the periphery of the specimen onto cork or thick paper. Too much tension on the specimen could result in artificially thinned lesions. Needles should not be placed directly through a lesion but at the margin. Besides patient data, an exact description on location should be provided (e.g. cms from anocutanous line), as well as size and morphology (stalked polyp, non-polypoid – Paris classification, etc.). Additional information about central depression or focal erosion or ulceration or coexistent chronic inflammatory bowel disease can be useful. Endoscopic pictures can also be submitted with the specimen(s).

7.6.2   Fixation

Fixation should be by buffered 10% formalin; this equals a roughly 4% paraformaldehyde concentration, as formalin is 30–40% paraformaldehyde. Specimen(s) can shrink due to formalin fixation, therefore measurements taken after fixation can differ from those prior to fixation. Fixation in alcohol is not recommended and if any other fixatives are used a comparative study of size of adenomas after fixation should be performed prior to use to avoid excessive shrinkage of adenomas to avoid under treatment.

7.6.3   Dissection

The pathologist should verify the complete removal of neoplastic lesions (clear margins) and the absence of submucosal invasion in biopsy specimens. Currently we recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. Cases of incomplete removal or uncertainty about submucosal invasion should be highlighted in the pathology report **(VI - B)**.[Rec 7.6] Lesion size should be given in millimetres. Size should be carefully measured identifying the maximum diameter of the adenomatous component as well as the distance to the margin of excision(s) to within a mm **(V - B)**.[Rec 7.8]

Given the small dimensions of the submucosal layer, infiltration into the submucosal level should be measured in microns from the bottom line of the muscularis mucosae **(VI - B)**.[Rec 7.8]

7.6.3.1   Polypoid lesions

Polyps must be sliced and totally embedded. Special attention should be paid to the resection margin, which should be identified and described (dot-like, broad, stalked, etc.) and either dissected tangentially into an extra cassette or sliced in a way that allows complete assessment.

7.6.3.2   Mucosal excisions

Mucosal excisions need to be pinned out on a cork board or on another suitable type of material, fixed, described and dissected allowing the identification of involvement of the deep and lateral surgical margins. Particular attention should be paid to any areas of ulceration or induration for signs of invasion. Inking margins is recommended.

7.6.3.3   Piecemeal removal

If it is possible to reconstruct a lesion removed piecemeal it may be helpful, but this is not commonly the case. It is good practice to embed the entire lesion to allow exclusion of invasive malignancy. Occasionally, whole embedding will not be possible.

7.6.4   Sectioning and levels

Three or more levels should be cut through each block and stained with haematoxylin and eosin.

7.6.5   Surgically-removed lesions

7.6.5.1   Classification

The staging of colorectal cancer can be undertaken by a number of different systems. The two used in Europe are TNM and the older Dukes classification. Originally the Dukes classification system placed patients into one of three categories (stages A, B, C) (see Table 7.2). This system was subsequently modified by dividing stage C into stage C1 and C2 and the addition of a fourth stage (D). More recently, the Union Internationale Contra le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) has introduced the TNM staging system, that places patients into one of four stages (Stage I-IV). TNM is superior to Dukes because of the greater information it yields, but there are currently major issues due to the periodic reclassification of this system that can lead to stage migration.

Table 7.2: Modified Dukes stage

Dukes A	Tumour penetrates into, but not through the muscularis propria (the muscular layer) of the bowel wall.
Dukes B	Tumour penetrates into and through the muscularis propria of the bowel wall but does not involve lymph nodes.
Dukes C	**C1**: There is pathological evidence of adenocarcinoma in one or more lymph nodes but not the highest node. **C2**: There is pathological evidence of adenocarcinoma in the lymph node at the high surgical tie.
Stage D	Tumour has spread to other organs (such as the liver, lung or bone).

TNM has a number of versions, so the version used should be noted in brackets (e.g. v5, v6, v7). Table 7.3 permits comparison of the most recent versions, 5, 6 and 7 (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009). However, there are differences between the versions, particularly regarding the notes on T and N classification. There is also variation between countries as to the TNM classification used. For example, TNM 5 is recommended in the United Kingdom, Holland, Belgium and Denmark and is growing in popularity in other countries.

In the USA version 7 is used. TNM 7 appears to be more subjective than TNM 5 due to the notes on N classification and the category N1c, promoting stage migration from II to III (Quirke et al. 2007; Jass et al. 2008; Quirke et al. 2010). National results should be reported with the version of TNM used in a given country **(VI - B).**[Rec 7.3]

Table 7.3: TNM classification of tumours of the colon and rectum

T – Primary Tumour	Clinical Classification	5th Edition (1997)	6th Edition (2002)	7th Edition (2009)
TX	Primary tumour cannot be assessed	+	+	+
T0	No evidence of primary tumour	+	+	+
Tis[1]	Carcinoma in situ: intraepithelial or invasion of lamina propria	+	+	+
T1	Tumour invades submucosa	+	+	+
T2	Tumour invades muscularis propria	+	+	+
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissues	+	+	+
T4[2,3]	Tumour directly invades into other organs or structures and/or perforates visceral peritoneum	+	+	+
T4a	Perforates visceral peritoneum	-	-	+
T4b	Directly invades other organ or structures	-	-	+
N – Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed	+	+	+
N0	No regional lymph node metastasis	+	+	+
N1	Metastasis in 1 to 3 regional lymph nodes	+	+	+
N1a	1 node	-	-	+
N1b	2-3 nodes	-	-	+
N1c	Satellites[4] in subserosa, *without* regional nodes	-	-	+
N2	Metastasis in 4 or more regional lymph nodes	+	+	+
N2a	4-6 nodes	-	-	+
N2b	7 or more nodes	-	-	+
M – Distant Metastasis				
MX	Distant metastasis cannot be assessed	+	+	-
M0	No distant metastasis	+	+	+
M1	Distant metastasis	+	+	+
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s))	-	-	+
M1b	Metastasis in more than one organ or the peritoneum	-	-	+

	Stage Grouping			5th Edition (1997)	6th Edition (2002)	7th Edition (2009)
Stage	T- Tumour	N - Node	M - Metastasis			
Stage 0	Tis	N0	M0	+	+	+
Stage I	T1,T2	N0	M0	+	+	+
Stage II	T3,T4	N0	M0	-	-	+
Stage IIA	T3	N0	M0	+	+	+
Stage IIB	T4	N0	M0	+	+	-
Stage IIB	T4a	N0	M0	-	-	+
Stage IIC	T4b	N0	M0	-	-	+
Stage III	Any T	N1,N2	M0	-	-	+
Stage IIIA	T1,T2	N1	M0	+	+	+

Stage	T- Tumour	N - Node	M - Metastasis	5th Edition (1997)	6th Edition (2002)	7th Edition (2009)
		Stage Grouping, cont'd				
Stage IIIA	T1,T2	N1c	M0	-	-	+
Stage IIIA	T1	N2a	M0	-	-	+
Stage IIIB	T3,T4	N1	M0	+	+	-
Stage IIIB	T3,T4a	N1/N1c	M0	-	-	+
Stage IIIB	T2,T3	N2a	M0	-	-	+
Stage IIIB	T1,T2	N2b	M0	-	-	+
Stage IIIC	Any T	N2	M0	+	+	-
Stage IIIC	T4a	N2a	M0	-	-	+
Stage IIIC	T3,T4a	N2b	M0	-	-	+
Stage IIIC	T4b	N1,N2	M0	-	-	+
Stage IV	Any T	Any N	M1	+	+	-
Stage IVA	Any T	Any N	M1a	-	-	+
Stage IVB	Any T	Any N	M1b	-	-	+

No.	5th Edition	6th Edition	7th Edition
		Notes	
1	Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intra-mucosal) with no extension through muscularis mucosae into the submucosa. (Note: the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis recommend not using this category. Respective lesions should be reported as mucosal high-grade neoplasia, see Section 7.3.)		
2	Direct invasion in T4 includes invasion of other segments of the colon or rectum by way of the serosa, e.g. invasion of sigmoid colon by a carcinoma of the cecum.		Direct invasion in T4b includes invasion of other organs or segments of the colon or rectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria
3		Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the classification should be pT3.	Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-T3, depending on the anatomical depth of wall invasion.
4	A tumour nodule greater than 3 mm in diameter in perirectal or pericolic adipose tissue without histological evidence of a residual lymph node in the nodule is classified as regional lymph node metastasis. However, a tumour nodule up to 3 mm in diameter is classified in the T category as discontinuous extension i.e. T3.	A tumour nodule in the pericolic/perirectal adipose tissue without histological evidence of a residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour it should be classified in the T category and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion.	Tumour deposits (satellites), i.e. macroscopic or microscopic nests or nodules, in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion with extra-vascular spread (V1/2) or a totally replaced lymph node (N1/2). If such deposits are observed with lesions that would otherwise be classified as T1 or T2, then the T classification is not changed, but the nodule is recorded as N1c. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node and not as a satellite, and each nodule should be counted separately as a lymph node in the final pN determination. (Note of the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis: introduction of N1c category leads to stage shift from II to III for some tumours)

7.6.5.2 Practical issues

High-quality reporting of colorectal cancer is very important both to the clinicians treating the patients and to the cancer registry. The introduction of a 'minimum' data proforma template allows more complete reporting compared with interpretation of free text reports by medical staff (Quirke & Williams 1998; Cross, Feeley & Angel 1998; Rigby et al. 1999; Branston et al. 2002; Oppong et al. 2002; Beattie et al. 2003; Wei et al. 2004; Eon et al. 2006). All biopsies and lesions identified in the screening programme and the subsequent resection specimens should be reported on a paper or electronic proforma **(II - B)** in a timely manner and in a minimum of 90% of all cases. The proforma should be sent to the referring physician, the relevant cancer registry and the screening programme **(VI - B).** [Rec 7.11]

Dissection should be according to national guidelines such as those for the United Kingdom; Royal College of Pathologists (Williams, Quirke & Shepherd 2007a; Williams, Quirke & Shepherd 2007b; Williams, Quirke & Shepherd 2007c) and the NHS Bowel Cancer Screening publication (NHS Bowel Cancer Screening Programme 2007), the Scottish clinical guidelines (SIGN 2003), the Dutch guidelines (Vereniging integrale kankercentra 2008a; Vereniging integrale kankercentra 2008b), the German guidelines (Schmiegel et al. 2008), or the Italian guidelines (Risio et al. 2006). For examples of these guidelines see the list of websites in Appendix 4 of the full Guidelines document. If national guidelines do not exist they should be created or adopted from elsewhere **(VI - B)**. An additional free text written report is optional, but needs to include all of the data required in the proforma **(VI - B).** [Rec 7.12]

Pathologists need access to a high-quality, binocular microscope with at least the following objectives: 5x, 10x, 20x and 40x and that fulfils national guidelines such as those of the Sector Committee for Pathology and Neuropathology of the German Accreditation Body (DAP-TM-30 2007).

A computer is required for identifying previous material from a given patient and for filling in proformas electronically and online if secure online services are available. Adequate time must be available for dissection, reporting, and attendance at meetings of the screening team and the colorectal cancer multidisciplinary team **(VI - B).** [Rec 7.17] Time and funding are required for pathologists to attend national meetings on the screening programme and continued training in histopathology of colorectal neoplasia. Pathologists should attend one refresher training course every year on the pathology of colorectal neoplasia to maintain quality. **(VI - B).** [Rec 7.22]

7.7 Standards and quality indicators

There should be good communication between members of the screening team with agreed terminology, regular meetings and clinical discussions **(VI - B).** [Rec 7.16]

An external quality assurance programme should be put in place, specifying a minimum of two slide circulations per year of an adequate number of slides **(VI - B).** [Rec 7.17] This may be via clusters or cells of pathologists using glass slides, or can be electronic using images or virtual slides (Risio et al. 2010) distributed via DVD or the web (see http://www.virtualpathology.leeds.ac.uk). There should be external oversight of such programmes. In the absence of evidence-based guidelines we recommend that pathologists reporting in a colonoscopy programme should not report high-grade neoplasia in more than 5% of lesions and those in an FOBT programme in not more than 10% of lesions **(VI - B).** [Rec 7.21]

The pathologists reporting in the programme must meet their national criteria for safety in reporting colorectal cancer **(VI - B)**.[Rec 7.19] Departments and pathologists taking part in screening programmes should audit their own reporting practices for key features, including the number of lymph nodes retrieved, the frequency of circumferential resection margin involvement (CRM) and the frequency of high-risk features such as extramural vascular invasion and peritoneal invasion reported **(VI - B)**.[Rec 7.18, 7.20] In the UK, national standards suggest that the number of nodes retrieved should be above a median of 12, CRM positivity in rectal cancer should be below 15%, extramural vascular invasion reported in more than 25%, and peritoneal invasion in more than 20%. The laboratory must be able to demonstrate participation in a laboratory technical external quality assurance programme, such as Clinical Pathology Accreditation UK (http://www.cpa-uk.co.uk/), the ISO/IEC accreditation developed by the Sector Committee for Pathology and Neuropathology of the German Accreditation Body (http://www.dakks.de/, see also Rocken & Manke (2010)), or other national standards **(VI - C)**.[Rec 7.23]

7.8   Data collection and monitoring

Lesions reported in the screening programme should be reported by proforma **(II - B)** or structured reporting, and the data returned to the screening programme or national tumour registries. This will include all lesions identified and the subsequent resection specimen. This should occur in a minimum of 90% of all cases **(VI - B)**.[Rec 7.11]

Studies have shown discrepancy between the histopathology of biopsies and total removal by polypectomy, EMR and surgical specimens. Colorectal cancer was detected in surgical specimens in over 20% of biopsies diagnosed with high-grade neoplasia (Gondal et al. 2005). Sub-mucosal invasion was detected in surgical specimens in over 25% of cases with mucosal neoplasia (Tominaga et al. 2009). Therefore the correlation between histological diagnosis of biopsies and resections should be reported. Any lack of correlation should be discussed by the multi-disciplinary team and the results of this discussion should be documented **(III - B)**.[Rec 7.13]

Pathologists must ensure that their proformas are received by the screening programme coordinators or a cancer registry for the purposes of clinical management, audit and quality assurance **(VI - B)**.[Rec 7.14]

Results from the key indicators of quality should be returned for analysis to the funding body: either the Health Authority or the national screening programme's offices **(VI - B)**.[Rec 7.14]

Statistics should include the frequency of colorectal cancer and the distribution of TNM stages and version used; as well as the distribution of the type of lesion, size, location, frequency of grades of dysplasia and villousness (villous, tubulo-villous or tubular) and presence of non-neoplastic lesions. **(VI - B)**.[Rec 7.15]

7.9 Images

A selection of images and digital slides showing the histopathology of lesions commonly detected in screening programmes, as well as some images illustrating pitfalls in histopathologic interpretation is provided in the internet at http://www.virtualpathology.leeds.ac.uk (go to: "European Guidelines for quality assurance in pathology in colorectal cancer screening and diagnosis - Imaging library"). The site has been created to establish an initial, quality-assured repository for images illustrating the present chapter. The images are provided for reference and have been reviewed by pathologists from at least three European countries. We encourage colleagues to submit further images which they feel could be instructive or otherwise useful in illustrating or further developing the European Guidelines.

We also aim to extend the scope of this site in the future to promote pan-European and international collaboration in training and in expanding the evidence base for further advances in colorectal cancer screening and diagnosis.

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

Annex

Annotations of colorectal lesions

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7A.1   Introduction

European Guidelines for quality assurance of pathology in colorectal cancer screening and diagnosis should provide multidisciplinary standards and best practice recommendations that can be implemented routinely across the EU. The authors therefore chose to limit the scope of Chapter 7 and to describe in greater detail in an annex some issues raised in the chapter, particularly details of special interest to pathologists. We also felt that an annex would be the appropriate place to point out new insights not yet widely adopted in Europe in routine practice that may be included in future updates of the Guidelines.

7A.2   Grading of neoplasia

In the present Guidelines, a classification system for colorectal neoplasia has been recommended based on a modified version of the revised Vienna classification (Section 7A.3). For readers not yet familiar with the Vienna classification, it may be helpful to note that it is the first classification to include a clinical recommendation for each neoplastic category. Furthermore, the system was developed to improve diagnostic reproducibility in the interpretation of biopsy specimens and subsequent resection specimens (Schlemper, Kato & Stolte 2000; Schlemper et al. 2000; Schlemper, Kato & Stolte 2001). Strictly speaking, the Vienna classification is only valid for biopsy specimens, since a clinical recommendation should follow. However, to avoid diagnostic inconsistencies, the Vienna classification can be used for resection specimens as well.

In the Vienna classification and hence in the European Guidelines, the term *neoplasia* rather than *dysplasia* is used to refer to epithelial tumours associated with chronic inflammatory diseases. Whereas the Vienna classification differentiates between strictly intraepithelial lesions and those involving the lamina propria, the European Guidelines only refer to *mucosal neoplasia* that may or may not involve the lamina propria (see Section 7A.3). More importantly, the EU Guidelines recommend a two-tiered grading of mucosal neoplasia. The pathologist must decide whether a neoplastic mucosal lesion can be categorised as low or as high grade; for criteria, see Table 7A.1.

As always in neoplasia, the lesion should reach the mucosal surface (no epithelial maturation). Undermining edges of an adjacent carcinoma should be excluded.

The criteria in Table 7A.1 can be weighted. The most important criteria for the diagnosis of carcinoma are the lateral expansion and the number of nuclear rows. In carcinoma, the number of nuclear rows should change within a single gland. High-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–5 nuclei, and the glands do not show lateral expansion. Low-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–3 nuclei (Wolber & Owen 1991; Ajioka et al. 1994; Ajioka et al. 2000).

In histopathology, the entity of carcinoma *in situ* is generally defined as carcinoma confined to the epithelial layer. In squamous epithelium such an entity can be readily diagnosed. In columnar epithelium, an analogous entity should theoretically also exist. However, to date there are no exact criteria that would permit diagnosis and that would enable the histopathologist to distinguish high-grade intraepithelial neoplasia from mucosal carcinoma that is invasive in the lamina propria. Therefore,

throughout the entire gastrointestinal tract, use of the term *carcinoma in situ* is not recommended for respective lesions in columnar epithelium. The term *intramucosal carcinoma* is widely introduced in the upper GI tract but not yet in the lower GI tract (see also Section 7A.4.5). We prefer the term mucosal neoplasia to intraepithelial neoplasia as high-grade dysplasia can contain epithelial neoplasia and invasion into the lamina propria according to the TNM classification.

Table 7A.1: Grading of gastrointestinal neoplasia

	Normal	Low-grade mucosal / intraepithelial neoplasia (LGMN)	High-grade mucosal / intraepithelial neoplasia (HGMN)	Invasive Cancer
Glands	non-branching	villous	branching, cribriform, irregular, solid	branching, cribriform, irregular, solid
Expansion	up/down	till surface	till surface	lateral expansion
Epithelial differentation	up/down	top-down and exceptional down-top	no maturation towards surface	
Goblet cells	+ +	(+)	-/(+) retronuclear, atypic	
Nuclear rows	1	2–3	2–5	changing
Nuclear size	small, basal	palisading	enlarged	vesicular
Chromatin	few	+	+ +	+ + / + + +
Nucleoli	none	none	few small	several/ prominent

Modified from (Borchard et al. 1991; Borchard 2000; Vieth & Stolte 2005)

7A.3 Classification of serrated lesions

7A.3.1 Terminology

The terminology is still under discussion. Serrated lesions can be regarded as a continuous spectrum of colorectal lesions with increasingly more pronounced serrated morphology starting with a *hyperplastic polyp* and progressing to *sessile serrated lesions* (*SSLs*, sometimes referred to as *sessile serrated adenomas* or *sessile serrated polyps*), *traditional serrated adenomas* (*TSA*), and leading, finally, to *adenocarcinoma*. Not only the adenomatous component but also other alterations associated with more pronounced serrated morphology may potentially progresses to cancer (see Table 7A.2).

The situation involving *sessile serrated lesion*s is complicated as these lesions only reveal complex structural abnormalities, not adenomatous changes. Therefore, these lesions are neither adenomatous

nor are they neoplastic. This is why Kudo et al. (2008) and Lambert et al. (2009) recommended that these lesions no longer be called adenomas; instead they should be referred to as *sessile serrated lesions* (SSLs). Few of these lesions are reported to rapidly progress to invasive carcinoma, (Oono et al. 2009). Those few cases that do progress rapidly, particularly in the right colon, may be expected to appear more frequently as interval cancers. *Traditional serrated adenomas* (TSAs), unlike SSLs, do contain adenomatous alterations, albeit sometimes quite subtle (Longacre & Fenoglio-Preiser 1990); they are therefore termed correctly and treatment and surveillance should correspond to that of adenomas (see Chapters 8 and 9).

Due to the continuous spectrum in the serrated pathway to colorectal cancer, lesions with combinations of serrated morphology and adenomatous cytology can be observed. If more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion, or at least one type in combination with adenomatous tissue, such lesions are referred to as *mixed polyps*.

The different histopathologic types (e.g. HP and SSL, SSL and TSA, adenoma and SSL, etc.) must be stated in the diagnosis.

Table 7A.2: Continuous spectrum of serrated lesions and possible combinations of histopathologic types. Every lesion can give rise to adenocarcinoma. Most of the adenocarcinomas are believed to derive from adenomatous components.

Lesion	Neoplasia	Risk of malignant transformation
Hyperplastic polyp	no	minimal
Sessile serrated lesion	no	slightly increased but exact data are missing (rapid transformation may be possible in a short time)
Traditional serrated adenoma	yes	increased and suggested worse prognosis than carcinomas arising in sessile serrated lesions
Mixed polyp	yes	increased, but exact data are not available
Adenoma (tubular, villous)	yes	increased, 17 years on average

7A.3.2   Hyperplastic polyp

Hyperplastic polyps (HPs) are composed of elongated crypts (no complex architecture) with serrated architecture in the upper half of the crypt. These polyps usually show some proliferation in the basal (non-serrated) part of the crypts (regular proliferation). Nuclei are small, regular, basal-orientated and lacking hyperchromasia, but with stratification of the upper (serrated) half of the crypts, and without cytological or structural signs of neoplasia.

Differences in the appearance of the cytoplasma permit recognition of three types:

- Microvesicular type (MVHP);
- Goblet-cell-rich type (GCHP); and
- Mucin-poor type (MPHP)

The microvesicular variant greatly predominates, but distinction between types is subject to wide interobserver variation, especially in small lesions, and is not always possible. Currently, routine sub-classification is therefore neither feasible, nor has it been shown to be beneficial.

At the molecular level the microvesicular variant of HP may be the precursor lesion for sessile serrated lesion, and a goblet-cell-rich HP may be the precursor lesion for a traditional serrated adenoma (Torlakovic et al. 2003; O'Brien 2007; O'Brien et al. 2008). Routine distinction of these types is not necessary.

7A.3.3 Sessile serrated lesion

Sessile serrated lesions are described in the literature as "sessile serrated adenoma" and are often found in the right colon. This is a misnomer since sessile serrated lesions do not contain adenomatous changes (Higuchi & Jass 2004; Kudo et al. 2008; Lambert et al. 2009).

To date, four synonymously used terms exist for these lesions: sessile serrated adenoma (Torlakovic & Snover 1996), superficial serrated adenoma (Oka et al. 2004), Type 1 serrated adenoma (Jaramillo, Tamura & Mitomi 2005), and serrated polyp with abnormal proliferation (Torlakovic et al. 2003).

We recommend using only the term *sessile serrated lesion* and avoiding use of any other terms for this entity. This recommendation is given in full awareness that sessile serrated lesions do not show histological signs of an adenoma, but, like adenomas, they should be excised if detected during an endoscopic examination. Currently even in the hands of expert GI pathologists the agreement on the sub-types of serrated lesions is only moderate (Wong et al. 2009).

The vast majority of SSLs will not progress to adenocarcinoma. Histological criteria of these sessile, usually larger lesions include an abnormal proliferation zone with structural distortion, usually most pronounced in dilatation of the crypts, particularly near the base. Abundant mucus production is usually also observed as pools of mucin in the lumen of the crypts and on the surface of the mucosa. SSLs are found mainly in the right colon and may be misdiagnosed as hyperplastic polyps. Clues to the correct diagnosis include location and large size. As discussed above, cytological signs of "neoplasia" are lacking, but structural abnormalities are present, i.e. glandular branching (Higuchi & Jass 2004).

Sessile serrated lesions have an elevated serration index and serration in the basal half of crypts with basal dilation of crypts. The epithelium/stroma-ratio is believed to be >50% in SSL. There is crypt branching with horizontal growth (above muscularis mucosae; e.g. T- and L-shaped glands) and often pseudoinvasion into the submucosal layer, rectangular dilation of whole crypts with and without presence of mucus, increased number of goblet cells at the base of the crypts, vesicular nuclei with prominent nucleoli and proliferation zone in the middle of the crypts. Currently there is insufficient evidence available in the literature for weighting of these criteria.

A well-oriented polypectomy is mandatory for the identification of such histological features. Correct assessment of the deepest portions of the mucosa is impossible in superficial or tangentially cut lesions (O'Brien 2007; O'Brien et al. 2008).

Further criteria include an often asymmetrical expansion of the proliferation zone into the middle third of crypts. Often mild cytological atypia (slightly enlarged vesicular nuclei, nucleoli) is found without clear signs of neoplasia (dysplasia).

BRAF-Mutations depend on the type and location of lesion (see Table 7A.3).

Other abnormalities include:

- The majority of SSL and TSA show CIMP and promoter methylation of hMLH1

- BRAF mutations in 8–10% of all CRC (27–76% of CIMP and sporadic MSI-H CRC)

- BRAF mutations in the majority of SSL and TSA (also microvesicular variant of HP, especially proximal), but rarely (0–5%) in adenoma. (Toyota et al. 1999; Toyota et al. 2000; Ogino et al. 2006; Jass 2007; Samowitz et al. 2007; Ogino et al. 2007; Shen et al. 2007; Grady & Carethers 2008; Kawasaki et al. 2008; Ogino & Goel 2008; Suehiro et al. 2008; Ogino et al. 2009).

Table 7A.3: Prevalence of serrated lesions with BRAF Mutation: A prospective study of patients undergoing colonoscopy

Lesion	**Number** (n=414) (% of all lesions)	**Proximal location** (% of BRAF mutations)	**Distal location** (% of BRAF mutations)
Hyperplastic polyp	120 (29%)	35 (29%)	85 (71%)
Sessile serrated lesion	36 (9%)	27 (75%)	9 (25%)
Trad. serrated adenoma	3 (1%)	2 (66%)	1 (33%)
Mixed polyp	7 (2%)	4 (57%)	3 (43%)
Tubular adenoma	237 (57%)	176 (74%)	61 (26%)
Villous adenoma	11 (3%)	6 (55%)	5 (45%)

Source: modified from (Spring et al. 2006)

The frequency of sessile serrated lesions in small retrospective series is estimated at 2–11% of all mucosal lesions in the colon (Jass et al. 2006; Carr et al. 2009); between 8% and 23% are misdiagnosed as hyperplastic polyps with an interobserver variation of up to 40% (Torlakovic et al. 2003; Goldstein et al. 2003; Montgomery 2004; Higuchi, Sugihara & Jass 2005).

Table 7A.4: Comparison of proliferative activity in adenoma, hyperplastic polyps, sessile serrated lesion and traditional serrated adenoma

Ki-67	Adenoma	Hyperplastic polyps	Sessile serrated lesion
upper 1/3	68.8%	0.1%	1.6%
middle 1/3	48.7%	9.1%	20.3%
lower 1/3	29.6%	60.3%	64.9%

Source: modified from (Higuchi, Sugihara & Jass 2005; Sheridan et al. 2006)

The histological features separating HPs from SSLs constitute a continuous spectrum, and intermingled features can often be seen. This could explain the moderate interobserver concordance

(k=0.47) and the overlapping proliferative activity, and may justify establishing semi-quantitative criteria for diagnosis (e.g. >30% of undifferentiated cells) (Sandmeier, Seelentag & Bouzourene 2007; Farris et al. 2008). Only a few immunohistochemical markers (Ki67, Ki67 + CK20, MUC6) have been tested for differentiating HPs and SSAs, and their usefulness in colorectal screening and diagnosis remains to be validated (Torlakovic et al. 2008; Owens, Chiosea & Kuan 2008). At present, such an additional immunohistochemical analysis cannot be recommended (see Table 7A.4).

In all likelihood, lesions formerly interpreted as *mixed hyperplastic and adenomatous polyp* are, in fact, SSLs complicated by conventional neoplasia (Sheridan et al. 2006). Special care must be taken in such cases to document the respective histopathologic components in such mixed polyps. Sometimes the conventional neoplastic part shows features other than in classical adenomas. The nuclei are prominent, less palisading and smaller than in classical adenomas. It is not clear whether this type of morphology is distinct for serrated lesions and whether any clinical implications can be drawn.

Prospective studies with risk stratification are needed to develop more precise methods of diagnosis and recommendations for classification. Sessile serrated lesions appear to take a long time (average 17 years) to develop into an invasive carcinoma. In contrast, an ill-defined, small subsample of SSLs seems to rapidly progress (Sheridan et al. 2006; Oono et al. 2009). Therefore, SSLs should be completely excised, particularly if they are located on the right side of the colon (O'Brien et al. 2008; Noffsinger 2009).

Diagnosis on a biopsy is not adequate to exclude SSL since the most severe histologic changes might only appear focally within a lesion that otherwise appears to be a hyperplastic polyp (Schreiner, Weiss & Lieberman 2010).

The German guidelines for colorectal cancer (Schmiegel et al. 2008) recommend complete removal and follow-up of SSL similar to adenomas. An intensive surveillance protocol is recommended for sessile serrated lesions (surveillance colonoscopy after 3–5 years subsequent to complete excision of non-neoplastic SSL, after one year following excision of SSL HGIEN (Schmiegel et al. 2008).

The UK guidelines (NHS Bowel Cancer Screening Programme 2007; Williams, Quirke & Shepherd 2007a; Williams, Quirke & Shepherd 2007b; Williams, Quirke & Shepherd 2007c) recommend complete excision but classify these lesions in the same risk category as hyperplastic polyps. The existing evidence base is not definitive as to the level of risk, and follow up decisions should be made locally until more evidence is forthcoming.

7A.3.4   Traditional serrated adenoma

Traditional serrated adenomas show neoplastic crypts with a serrated structure (WHO 2000). Compared to hyperplastic polyps, the most striking diagnostic feature of traditional serrated adenomas are the complex serrated morphology and the eosinophilic, "dysplastic" cytoplasm that still can be identified in cases with invasive adenocarcinoma. These lesions also frequently show *BRAF* mutations and CIMP with *hMLH1*.promoter.methylation. Additionally, so-called intraepithelial microacini can be observed in the upper half of the mucosa (ectopic crypt formation). Often these lesions are located in the distal colon and can be found more frequently in elderly female individuals (Longacre & Fenoglio-Preiser 1990; Higuchi & Jass 2004; Torlakovic et al. 2008).

7A.3.5 Mixed polyp

A mixed polyp may contain partially hyperplastic, classical adenomatous or traditional serrated adenoma or sessile serrated lesion components. Rather than a continuous spectrum such lesions most probably represent several evolutionary lines, depending on the order of certain abnormalities in genes such as APC, BRAF and KRAS (O'Brien 2007; O'Brien et al. 2008). It has to be determined whether mixed polyps represent serrated lesions complicated by conventional neoplasia (Snover et al. 2005).

Focal, hyperplastic-like narrowing of the basal region of a few crypts in SSL and the findings of flat sectors or *ectopic crypt formation* in SSL/TSA (Torlakovic et al. 2008) are examples of combinations of serrated and adenomatous components. However, these features add no information of further diagnostic value; they probably result from the continuous developing nature of serrated lesions. We therefore recommend that the diagnosis of *mixed polyp* should be restricted to the definition given in Section 7A.3.1. Mixed polyps are serrated lesions in which more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion or at least one type in combination with classical (unserrated) adenomatous tissue. The different histopathological types must be mentioned in the diagnosis, e.g. mixed polyp (HP and SSL, adenoma and SSL).

7A.3.6 Risk of progression

The vast majority of hyperplastic polyps and serrated lesions will not undergo malignant transformation. Only a fraction, especially in the group of sessile serrated lesions, may progress to rapidly aggressive carcinoma (Spring et al. 2006; Carr et al. 2009).

Hyperplastic polyps rarely progress to carcinoma. A single case report can be found in the literature (Watanabe & Suda 1984) and a second (unpublished) case has been reported in southern Germany. Interestingly, these carcinomas show features of gastric differentiation.

Little evidence is available on which the risk of colorectal cancer associated with serrated lesions other than hyperplastic polyps could be reliably judged. The risk assessment for sessile serrated lesions is not yet defined, but a subset of these lesions appears to give rise to carcinoma often less than a few millimetres in size. In a series of 110 traditional serrated adenomas, 37% exhibited foci of significant neoplasia and 11% contained areas of intramucosal carcinoma (Longacre & Fenoglio-Preiser 1990). Mixed polyps (e.g., HP/TSA/SSL or HP/adenoma) seem to have at least the same rate of progression to colorectal carcinoma as adenomas, and the risk might be higher (Leggett et al. 2001; Hyman, Anderson & Blasyk 2004).

7A.4 Assessment of T1 adenocarcinoma

Careful assessment in T1 adenocarcinoma is mandatory because a decision is required on local excision or a major operation.

7A.4.1   Size

Firstly, accurate measurement is very important, and measurement must be to the nearest mm (and not rounded-up to the nearest 5 or 10 mm). The maximum size of the lesion should be measured from the histological slide and if the lesion is disrupted or too large, from the formalin-fixed macroscopic specimen. If a biopsy is received it should be stated that size cannot be assessed.

7A.4.2   Tumour grade

Poorly differentiated carcinomas are identified by the presence of either irregularly folded, distorted and often small tubules, or the lack of any tubular formation and showing marked cytological pleomorphism. In the absence of good evidence, we recommend that a grade of poor differentiation should be applied in a pT1 cancer when ANY area of the lesion is considered to show poor differentiation. It should be noted that this is not in accordance with the WHO classification that recommends a certain proportion of lesion showing poor differentiation before diagnosing a lesion as G3. Poor differentiation includes undifferentiated and poorly differentiated as defined by the WHO classification (Washington et al. 2009).

7A.4.3   Budding

Budding describes the biological behaviour of the tumour at the front of invasion (Deinlein et al. 2003). Budding or tumour cell dissociation (Gabbert et al. 1992) can be divided into slight, moderate and marked and is known from the Japanese literature of the 1950s (Imai 1954) and 1990s (Kobayashi et al. 1994).

At this time, evidence is lacking concerning reproducibility of the numerous methods for tumour budding measurement (see Table 7A.5). It is good practice but not mandatory to document the presence or absence of single tumour cells at the front of invasion, and we therefore recommend providing this additional information in the written report with an explanatory comment, as budding has been suggested as a prognostic factor in colorectal cancer (Nakamura et al. 2008; Ogawa et al. 2009; Sy et al. 2010).

7A.4.4   Site

The site of origin of each specimen should be individually identified by the clinician and reported to the pathologist on the histopathology request form. The pathologist should record this on the proforma. This is important information because the risk of lymph node metastasis from a T1 adenocarcinoma varies depending on the site and size of the lesion (rectum vs. other locations) (Poeschl et al. 2010).

Table 7A.5: Measurement of tumour budding.
Source: modified from (Konishi & Morson 1982; Haggitt et al. 1985; Cooper et al. 1995; Volk et al. 1995; Nascimbeni et al. 2002; Ueno et al. 2004; Nakamura et al. 2008)

Author	Year	pT	Count	Magnif.	Object.	Area (mm2)	Classification	Cut-off	Notes
Ueno	2004		H&E		20x	0,785	negative/positive	5	
Ueno	2002		H&E		25x	0,385	<10/>10	10	degree of grading agreement
Ueno	2004		H&E	250	25x	0,385	low (<10)/high (>10)	10	
Shinto	2005		IHC:MNF 116		20x		low (<10)/high (>10) moderate (10-19), severe (>20)		identification of cytoplasmic fragments
Shinto	2006	3	IHC:MNF 116		20x		low (<10)/high (>10) moderate (10-19), severe (>20)		scoring of cytoplasmic fragments called now podia
Okuyama	2002	1 and 2	H&E	n.a.	n.a.	n.a.	present/absent	1	endoscopically resected tumors were excluded
Okuyama	2003	3	H&E	n.a.	n.a.	n.a.	present/absent	1	
Okuyama	2003	3	H&E	n.a.	n.a.	n.a.	present/absent	1	
Prall	2005		IHC:MNF 116	250		0,785	low/high	25	ROC metastatic progression; 0-120 buds range; 14 median 20,46 mean
Kazama	2006	1	IHC: CAM5.2 and AE1/AE3	n.a.	n.a.	n.a.	present/absent	1	
Kanazawa	2007		H&E	n.a.	n.a.	n.a.	none/mild/ moderate/marked		
Nakamura	2008		H&E	n.a.	n.a.	n.a.	None/mild/ =low moderate/marked=high		
Choi	2007	2 or more	H&E		20x		(0-3)/(4-5)/(6-10)/(11-38)		
Park	2005	2 or more	H&E		20x		(0-3)/(4-5)/(6-9)/(10-38)		
Hori	2005		H&E	200	40x			0,05	mean intesity: (+/-SD) 6,6+/-5,6
Yasuda	2007		H&E				present/absent		5% of the horizontal length of the invasive front
Ishikawa	2008		IHC:MNFIb	400			negative/positive	5	

7A.4.5   Definition of invasion

In columnar epithelium, it is difficult to define the onset of invasive carcinoma and reliably distinguish it from high-grade intraepithelial neoplasia. Criteria such as single tumour cells are more likely to be seen in more advanced carcinomas, but not in early carcinomas. Desmoplastic stromal reactions are also seldom seen in very early carcinomas. However, basal membrane structures are frequently discernible in well-differentiated early carcinomas (Borchard et al. 1991; Borchard 2000; Vieth & Stolte 2005), so that definitions using "invasion through the basement membrane" are incorrect.

The WHO definition of adenocarcinoma in use when the EU Guidelines were developed excluded diagnosis of intramucosal carcinoma in the colon or rectum, in contrast to the accepted WHO definitions for the stomach, oesophagus and small bowel. In the latter cases, a decision on surgical vs. local therapy is made based on respective protocols. Comparable lesions in the colon and rectum are reported as high-grade mucosal neoplasia because a carcinoma in the colon is defined by infiltration of the submucosa according to the WHO classification.

The discussion on this issue among the authors of the pathology chapter in the EU Guidelines reflects, among other things, concern about potential overtreatment of early T1 carcinomas which are detected much more frequently in a screening setting. The clinical management of a lesion where invasion of the lamina propria has occurred is no different from that where high-grade changes are confined to the glands. This legitimate concern as to increased morbidity and mortality due to miscommunication of diagnostic criteria may be dealt with more effectively in the future, as multidisciplinary management of lesions detected in and outside of screening programmes advances. The authors hope that such advances and their effective dissemination will be stimulated by the publication of the new EU guidelines. This, in turn, may lead to revision of the current WHO definition of colorectal adenocarcinoma in a future revision of the WHO classification of gastrointestinal tumours. Pathologists should report on what version of the WHO and TNM classifications their diagnosis is based.

In those cases in which intramucosal colorectal cancer is suspected, and particularly in countries in which this diagnosis is documented in addition to the WHO terminology, explicit comments by the pathologist are recommended. Based on the cytological characteristics of the case, the pathologist should indicate whether local endoscopic or surgical removal is recommended, and the basis for this recommendation should be indicated. This recommendation should be discussed in a multidisciplinary conference prior to surgery. The Japanese criteria for such stratification have been published by Watanabe & Suda (1984). The updated Paris classification based on a workshop in February 2008 in Kyoto (Kudo et al. 2008) permits such subclassification based on improved grouping and explains in detail the grading criteria (Lambert et al. 2009).

The use of the term colonic carcinoma in situ introduced by the TNM system is inadequate because the criteria are too vague and cannot be used for columnar epithelium.

A subclassification of all carcinomas into low risk and high risk based on risk of lymph node involvement should always be undertaken. For exact criteria, please see Chapter 7 and the updated Paris classification (Kudo et al. 2008; Lambert et al. 2009).

Perineural invasion

Perineural invasion (PNI) was recently described as an independent risk factor for colorectal cancer (Liebig et al. 2009a; Poeschl et al. 2010). PNI is significantly associated with high tumour stage, grade and metastases. Furthermore, PNI serves as an independent predictor of disease-free and cancer survival (Liebig et al. 2009a; Poeschl et al. 2010). Recently, an association with other criteria indicating an aggressive course of disease, such as lymphatic vessel permeation, venous invasion, tumour growth pattern and budding (Jass, Love & Northover 1987) were described by Poeschl et al. (2010). Also, it was described that PNI-positive tumours are more likely to be incompletely resected and more

likely to progress after Mayo regimen chemotherapy than PNI-negative tumours. Lately Poeschl et al. were able to show that PNI is an additional independent factor for local tumour relapse.

It is recommended to record PNI in routine sections of colorectal cancer. According to recent studies (Liebig et al. 2009a; Liebig et al. 2009b; Poeschl et al. 2010; Marshall et al. 2010) immuno-histochemistry or special stains are not necessary to detect PNI. Prospective studies are needed to show the clinical relevance of PNI, its relationship to other features such as lymphatic and vascular invasion and the benefit of alternative treatment for such more aggressive tumours that are PNI positive.

7A.5 References

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8

Management of lesions detected in colorectal cancer screening

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Recommendations[1]

General requirements for treatment of colorectal cancer and pre-malignant lesions

8.1   Colorectal neoplasia should be managed by a multi-disciplinary team **(VI - A)**.[Sect 8.2]

8.2   The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95% of cases should be no more than 31 days **(VI - B)**. [Sect 8.2]

8.3   Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding superficial lesions (see Ch. 5) **(VI - A)**.[Sect 8.2; 5.1.2]

Management of pre-malignant colorectal lesions

8.4   Pre-malignant lesions detected at screening endoscopy should be removed **(III - A)**.[Sect 8.3]

8.5   Lesions that have been removed should be retrieved for histological examination (see also Ch. 7, Rec. 7.11) **(VI - A)**.[Sect 8.3.5; 7.6.5.2; 7.8]

8.6   Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy (See Chap. 6, Rec 6.13) **(V - A)**.[Sect 8.3]

8.7   Large sessile lesions of the rectum should be considered for transanal surgical removal **(II - B)**.[Sect 8.3.4]

8.8   For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the recommended method of local excision **(II - B)**.[Sect 8.3.4]

8.9   Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V - B)**.[Sect 8.3.3]

8.10   Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI - A)**.[Sect 8.3]

8.11   Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V - C)**.[Sect 8.3.7]

8.12   In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B)**.[Sect 8.3.7]

8.13   In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B)**.[Sect 8.3.7]

8.14   In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C)**.[Sect 8.3.7]

8.15   Aspirin therapy can **(IV – C)** - and in patients with stents should - be continued prior to and during polypectomy **(VI – B)**.[Sect 8.3.7]

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

Management of pT1 colorectal cancer

8.16   If there is clinical suspicion of a pT1 cancer, a site of excision should be marked with sub-mucosal India ink **(VI - C)**.^{Sect 8.4.1}

8.17   Where a pT1 cancer is considered high-risk for residual disease consideration should be given to completion colectomy along with radical lymphadenectomy, both for rectal cancer **(II - A)** and colon cancer **(VI - A)**. If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7, Rec. 7.7) **(VI - B)**.^{Sect 8.4.2; 7.5.3}

8.18   After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A)**. The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9, Rec. 9.16) **(III - B)**.^{Sect 8.4.3; 9.5.1}

Management of colon cancer

8.19   If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of colectomy **(VI - B)**.^{Sect 8.5.1}

8.20   Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B)**. Routine chest CT is not recommended **(III - D)**.^{Sect 8.5.1}

8.21   Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A)**.^{Sect 8.5.2}

8.22   Where appropriate, laparoscopic colorectal surgery should be considered **(I - A)**.^{Sect 8.5.2}

Management of rectal cancer

8.23   If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of excision of the rectal cancer **(VI - B)**.^{Sect 8.6}

8.24   Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI - B)**. Routine chest CT is not recommended **(III - D)**.^{Sect 8.6.1}

8.25   Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C)**.^{Sect 8.6.1}

8.26   All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II - A)** by an adequately trained specialist surgeon **(VI - A)**.^{Sect 8.6.3}

8.27   Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I - B)**.^{Sect 8.6.3}

8.28   All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I - A)**.^{Sect 8.6.2}

8.29   Local excision alone should only be performed for T1 sm1 rectal cancers, and if the patient is fit for radical surgery **(III - B)**.^{Sect 8.6.5}

8.30   In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III - B).** [Sect 8.6.5]

8.31   In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C).** [Sect 8.6.5]

8.32   If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II- B).** [Sect 8.6.5]

8.1   Introduction

Mortality reduction for colorectal cancer is the main endpoint of any colorectal screening programme but it must be appreciated that all screening modalities will detect substantial numbers of individuals with adenomas (Levin et al. 2008) as well as a lesser number of lesions in the serrated pathway, some of which should be treated as adenomas (see Ch. 7, Sect. 7.1, 7.2 and 7.2.4).[2] As adenomas are recognised to be pre-malignant (Leslie et al. 2002) screening has the potential to reduce the incidence of the disease if these lesions are adequately managed. To achieve the dual aims of mortality and incidence reduction it is essential that all the elements of the screening service achieve and maintain high levels of quality. The screening process can only be successful if it is followed by timely and appropriate management of screen-detected lesions.

In essence the management of screen-detected adenomas and carcinomas does not differ, stage for stage, from that required for symptomatic disease with the proviso that sub-optimal management can negate the benefit of screen detection. Screening does however detect a different spectrum of disease compared with that diagnosed in the symptomatic population (i.e. higher proportion of early disease) and there are some considerations in the management of screen-detected disease that should be emphasised. In this Chapter of the EU Guidelines the management of **endoscopically detected pre-malignant lesions, pT1 cancers**, as well as **colon cancer and rectal cancer** which is not limited to the submucosa are dealt with separately and discussion is focused on issues pertinent to screening. Accordingly, adjuvant chemotherapy and the management of advanced disease are not discussed.

8.2   General requirements for treatment of colorectal cancers and pre-malignant lesions

It is widely agreed that colorectal neoplasia is best managed by a multi-disciplinary team with expertise in surgery, endoscopy, pathology, radiology, radiotherapy, medical oncology, specialist nursing, genetics and palliative care (SIGN 2003), working in close collaboration with primary care **(VI - A).**[Rec 8.1] The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days (NHS 2007) **(VI - B).**[Rec 8.2] It should be noted that colonoscopy is not merely a diagnostic procedure, but has therapeutic capacity (Cotton & Williams 1996), and it is essential that the endoscopist carrying out screening colonoscopy has the necessary expertise to remove all but the most demanding polyps (see Ch. 5, Sect. 5.1.2) **(VI - A).**[Rec 8.3]

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[2] Serrated lesions can be classified as hyperplastic polyp, sessile serrated lesions, traditional serrated lesions and mixed polyps. The hyperplastic polyp must be distinguished from other serrated lesions due to its extremely low malignant potential. The significance of other lesions in the serrated spectrum is controversial and our knowledge is still developing. Hyperplastic polyps are non-neoplastic and their complete removal is optional. All other lesions in the serrated pathway should be excised and serrated lesions with neoplasia should be followed up (surveillance) as if they were adenomas (Ch. 7, Sect. 7.1, 7.2 and 7.2.4, Rec. 7.10).

Recommendations

- Colorectal neoplasia should be managed by a multi-disciplinary team **(VI - A).**[Rec 8.1]

- The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95% of cases should be no more than 31 days **(VI - B).**[Rec 8.2]

- Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding lesions (see Ch. 5, Sect. 5.1.2) **(VI - A).**[Rec 8.3]

8.3 Management of pre-malignant colorectal lesions

(Note: the terms "pre-malignant lesion" and "polyp" are used in the following text as it is impossible to be certain of the histology of colorectal lesions prior to removal, although the intention is to treat adenomas and in some cases also serrated lesions with neoplasia or the potential to develop neoplasia, as mentioned in Section 8.1.)

There is abundant evidence that colorectal adenomas are pre-malignant (Leslie et al. 2002), and it follows that a lesion found during colonoscopy that could be an adenoma should be removed **(III - A).**[Rec 8.4] Lesions should only be removed by endoscopists with adequate training in techniques of polypectomy, (see Chapter 6, Rec. 6.13) **(V - A).**[Rec 8.6]

For the purposes of management, polyps may be classified as small (≤5 mm), pedunculated, large (≥10 mm) sessile colonic and large sessile rectal. Patients with large adenomas not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**[Rec 8.10]

8.3.1 Small lesions

In order to obtain a representative histological specimen and to achieve definitive treatment, lesions >5 mm are removed by snaring. Those ≤5 mm may be removed with biopsy forceps or cold snaring. Hot biopsy forceps may be used to ensure destruction of polyp tissue when the endoscopist is not confident about removing all the abnormal tissue with ordinary forceps. One randomised controlled trial has compared hot biopsy with cold biopsy followed by bipolar coagulation and concluded that both were equally effective and safe (Paspatis et al. 2005). There is also evidence that hot biopsy is associated with a higher risk of haemorrhage than cold biopsy, particularly in the right colon (Weston & Campbell 1995; Parra-Blanco et al. 2000). Cold snaring may also be used safely for polyps ≤6 mm (Uno et al. 1997; Deenadayalu & Rex 2005).

Lesions <10 mm do not usually present major technical difficulties in endoscopic excision by snare electrocoagulation. It should however be born in mind that, particularly on the right side of the colon, the muscle wall is thin and even with small polyps (when they are sessile) sub-mucosal injection of saline is necessary to elevate the adenoma away from the underlying muscle wall prior to excision (Cotton & Williams 1996).

8.3.2   Pedunculated adenomas/polyps

The polyp on a stalk or the pedunculated adenoma is usually amenable to snare excision even when very large (≥20 mm) (Church 2003; Perez Roldan et al. 2004). In most instances it is appropriate to apply snare electro-coagulation directly to the stalk of the adenoma (Dell'Abate et al. 2001) . However, in those with thick stalks, and certainly those where the stalk is greater than 10 mm in diameter, pre-injection with 1 in 10 000 adrenaline (Hsieh et al. 2001) or the placement of a detachable nylon loop around the stalk below the site of coagulation (Brandimarte & Tursi 2001) can reduce the risk of bleeding. There is evidence from a randomised controlled trial that pre-injection with adrenaline is effective in reducing immediate bleeding after polypectomy (Hsieh et al. 2001).

If after transection of the stalk arterial bleeding is seen the stalk is grasped with the diathermy loop and held (without electro-coagulation) for 5 minutes; this should at least temporarily control the bleeding. The stalk can then be injected with adrenaline and scleroscent or nylon loop can be placed around the stalk remnant. Depending on the size and position of the stalk, the placement of one or two clips may be used as an alternative (Cotton & Williams 1996).

8.3.3   Large sessile colonic adenomas/lesions

With large sessile colonic lesions the choice is between formal surgical resection of the affected part of the colon and endoscopic resection at colonoscopy. The decision as to which strategy to adopt will depend on the ability of the colonoscopist and the availability of a tertiary referral centre where advanced endoscopic techniques can be used (Perez Roldan et al. 2004) **(V - B).**[Rec 8.9]

For sessile adenomas up to about 20 mm, complete excision may be possible using snare electro-coagulation after elevating the lesion by sub-mucosal injection of saline or saline plus adrenaline. The saline injection has two main functions; firstly, elevating the lesion facilitates the placement of a snare around it, and secondly, it protects the underlying muscle from damage thereby reducing the risk of perforation. For lesions >20 mm a similar technique may be employed but piecemeal excision is necessary (Doniec et al. 2003; Stergiou et al. 2003), and argon plasma coagulation can be used as an adjunct to this technique in order to destroy residual adenoma tissue (Garcia et al. 2004; Boix et al. 2007). If a lesion does not lift with sub-mucosal injection, snaring should not be attempted as this indicates involvement of the underlying muscle (Cotton & Williams 1996). For large carpeting lesions, endoscopic sub-mucosal resection using elevation with saline and a specially designed sheath for the colonoscope and a needle knife may be possible (Jameel et al. 2006). It must be appreciated, however, that this is a very advanced technique and at the present time it is only available in a few specialist tertiary referral centres.

8.3.4   Large sessile rectal adenomas/lesions

While sessile rectal adenomas ≤20 mm in diameter may be treated by snare electro-coagulation as described for colonic adenomas, the very large carpeting lesions may be treated by surgical transanal excision **(II - B).**[Rec 8.7] For low lesions this may be achieved using conventional transanal techniques utilising specifically designed retractors (e.g. the Pratt Bivalve Retractor, the Lone Star Retractor). For lesions of the mid and upper rectum however where access using conventional techniques is difficult either endoscopic sub-mucosal dissection (ESD) or transanal endoscopic microsurgery (TEM) may be employed. There is evidence from a randomised controlled trial that TEM results in less local recurrence than conventional local excision (Middleton, Sutherland & Maddern 2005) **(II - B).**[Rec 8.8] In

some situations where there is very extensive carpeting of the rectum it may be necessary to carry out a total proctectomy. Reconstruction can then be effected by means of a hand-sewn colo-anal anastomosis.

8.3.5   Retrieval of lesions

Whenever a lesion has been removed endoscopically it should be retrieved for histological examination firstly to assess the completeness of excision and secondly to confirm the benign nature of the lesion **(VI - A).**[Rec 8.5] Under most circumstances it is feasible to trap the excised lesion using the snare and to retrieve it in this fashion. Very small polyps may be retrieved by applying suction to the biopsy channel and employing a polyp trap. When there are multiple lesions or multiple fragments of a lesion, specifically designed endoscopic retrieval bags (e.g. Rothnet) can be employed (NHS 2007).

8.3.6   Management of incomplete endoscopic excision

Incomplete excision is most common when a large sessile lesion has been removed piecemeal, but it may occur in any situation. If residual lesion tissue is seen at the time of initial polypectomy, this should be excised using snare electrocoagulation where possible. Small areas of residual tissue that are not amenable to snare electrocoagulation may be treated with direct electrocoagulation or obliteration using argon beam therapy (Brooker et al. 2002; Regula et al. 2003; Boix et al. 2007).

If there is doubt about completeness of excision at the time of initial polypectomy or if the subsequent histopathology report indicates that there may have been incomplete excision, a repeat endoscopic examination of the treated area should be carried out within 3 months. Residual abnormal tissue seen at that time can be treated as outlined above. In the situation where residual adenoma is impossible to eradicate, surgical resection of the affected part of the large bowel may be required.

8.3.7   Management of pre-malignant lesions in patients taking anti-coagulants/anti-aggregants

Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V - C).**[Rec 8.11] The existing evidence (Timothy et al. 2001; Hui et al. 2004; Yousfi et al. 2004; Friedland & Soetikno 2006; Kim et al. 2006; Makar & Ginsberg 2006; Kimchi et al. 2007) relating to management of anticoagulants and antiplatelet therapy in patients undergoing endoscopic procedures is summarised in recent guidelines (Veitch et al. 2008) and indicates that the use of anticoagulants (warfarin) is associated with the significantly increased risk of bleeding after polypectomy while the use of aspirin or other NSAIDS or antiplatelet agents is not. However, the potent antiplatelet agent clopidogrel may pose a risk, especially in combination with aspirin, and although the available data are scarce, caution is advised. The following issues must be considered when deciding the management of patients taking anti-coagulants or anti-platelet therapy:

- The risk of discontinuing anti-coagulation;

- The bleeding risk associated with polypectomy;

- The morbidity and mortality rates of thromboembolic complications versus those of bleeding complications; and

- The timing of cessation and reinstitution of anti-coagulants or anti-platelet therapy.

Warfarin is discontinued 3 to 5 days before the procedure. Patients at high-risk of thromboembolic events receive subcutaneous low-molecular-weight-heparin (LMWH) which is stopped at least 8 hours before the procedure. The LMWH can be resumed 6 hours after the procedure.

Another option is to perform an initial diagnostic colonoscopy followed if necessary by a second colonoscopy for polypectomy using LMWH bridge therapy. If the high-risk of thromboembolism is potentially transient (e.g. deep venous thrombosis), the best option is to delay the polypectomy until the risk is decreased.

Ideally, and certainly until further evidence is available relating specifically to polypectomy, individuals taking clopidogrel must stop this medication at least 7 days before polypectomy is performed where it is safe to do so. However, in patients with coronary stents, stopping clopidogrel within 1 month for bare stents and within 12 months for drug-eluting stents carries a high-risk of acute thrombosis of the stent and myocardial infarction. In patients such as these, endoscopic polypectomy must be delayed for the appropriate period of time **(V - B)**.[Rec 8.12; 8.13] In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C)**.[Rec 8.14] Aspirin therapy can **(IV - C)** - and in patients with stents should - be continued **(VI - B)**.[Rec 8.15]

8.3.8   Synopsis

Summary of evidence

- Colorectal adenomas are recognized as pre-malignant **(III)**.

- Colonic adenomas can be removed by biopsy forceps, cold snaring, electrocoagulation snares or, when large and sessile, by endoscopic sub-mucosal resection **(V)**.

- Rectal adenomas, when not suitable for colonoscopic excision, can be removed by surgical trans-anal excision with or without the use of transanal endoscopic microsurgery (TEM) or endoscopic sub-mucosal dissection (ESD) **(II)**.

- Large colonic or rectal adenomas can be treated by surgical resection of the affected area if endoscopic resection is not possible **(V)**.

- The use of sub-optimal technique for polypectomy can result in perforation with attendant morbidity and mortality **(V)**.

- Removal of adenomas in an anticoagulated patient can result in potentially fatal haemorrhage **(V)**.

- Stopping clopidogrel within 1 month of the placement of bare coronary stents can result in acute thrombosis of the stent and myocardial infarction **(III)**.

- Stopping clopidogrel within 12 months of the placement of drug-eluting coronary stents can result in acute thrombosis of the stent and myocardial infarction, **(III)** although if absolutely essential it *may* be stopped temporarily at 6 months **(IV)**.

Recommendations for management of colorectal pre-malignant lesions

- Pre-malignant lesions detected at screening endoscopy should be removed **(III - A)**.[Rec 8.4]

- Lesions that have been removed should be retrieved for histological examination **(VI- A)**.[Rec 8.5]

- Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy **(V - A)**.[Rec 8.6]

- Large sessile lesions of the rectum should be considered for transanal surgical removal **(II - B)**.[Rec 8.7]

- For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the preferred method of local excision **(II - B).**[Rec 8.8]

- Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V - B).**[Rec 8.9]

- Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**[Rec 8.10]

- Appropriate precautions should be taken prior to endoscopic excision in patients on anticoagulants **(V - C).**[Rec 8.11]

- In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Rec 8.12]

- In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Rec 8.13]

- In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C).**[Rec 8.14]

- Aspirin therapy can **(IV - C)** and in patients with stents should - be continued prior to and during polypectomy **(VI - B).**[Rec 8.15]

8.4 Management of pT1 cancers

8.4.1 Primary management

A pT1 cancer can be defined as an invasive cancer that is confined to the submucosa. pT1 cancers are also commonly referred to as polyp cancers because they are generally detected and removed endoscopically. Although the evidence base relating to the management of these lesions is weak (Bentrem et al. 2005; Endreseth et al. 2005; Hahnloser et al. 2005; Floyd & Saclarides 2006; Chok & Law 2007), there has been one narrative review of this subject, and the recommendations given here are derived from the evidence cited in this review (Mitchell & Haboubi 2008).

The primary management of a pT1 cancer is, by definition, identical to that of an adenoma (see Sect. 8.3). In most cases the diagnosis of pT1 cancer is made on histological examination of the endoscopically excised lesion but the following features raise the suspicion of a polyp cancer:

- Lesion is larger than 20 mm;

- Lesion is uncharacteristically hard; or

- Lesion is ulcerated.

Identification of a previous polypectomy site may be difficult and can cause problems for the surgeon in deciding on the anatomical region to be removed if completion surgery (see below) is required. This problem can be overcome by injecting India ink sub-mucosally at the site of a suspected pT1 cancer at the time of its removal **(VI - C).**[Rec 8.16] India ink tattooing should be performed distal to the lesion and include at least three quadrants of the bowel. Care should be taken to avoid "Indian ink peritonitis" by initial raising of the mucosa with saline.

pT1 cancers can be categorised into low-risk and high-risk lesions according to their likelihood of being associated with lymph node metastases:

- Low risk: Well or moderately differentiated and no lymphovascular invasion; rate of lymph node metastases <5%

- High risk: Poorly differentiated and/or lymphovascular invasion; rate of lymph node metastases ~35%

The significance of venous invasion is currently unknown.

8.4.2   Completion surgery

Patients with a histologically confirmed, completely removed low-risk pT1 cancer do not require additional surgery, due to their low risk of lymph node metastases. In patients with a high-risk polyp cancer with clear margins (RO), the multidisciplinary team should be consulted on whether completion surgery involving removal of the part of the large bowel in which the polyp was situated, along with radical lymphadenectomy, for both rectal cancer **(II - A)** and colon cancer **(VI - A)** is recommended. [Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist, as variation exists in evaluating high risk features (See also Ch. 7, Sect. 7.5.3 and Rec. 7.7) **(VI - B)**.[Rec 8.17] The precise nature of the surgery will of course depend on the site of the pT1 cancer. It may be difficult to precisely locate the site of the previous polypectomy and for this reason inking of the site at the time of initial polypectomy is advised when there is any clinical suspicion of polyp cancer (see above).

It should be noted that if a suspected pT1 cancer has been *incompletely* removed, lack of invasion beyond the submucosa cannot be guaranteed, and thus even in the situation where the lesion is well or moderately differentiated with no lymphovascular invasion, further treatment is required. This will usually take the form of completion surgery, although repeat endoscopic excision may be possible and appropriate in some situations.

In summary, current consensus would classify a pT1 cancer as high-risk requiring completion surgery in the following circumstances:

- When invasive cancer is seen at or within 1 mm of the resection margin;

- Where the cancer is poorly differentiated; or

- Where there is evidence of lymphovascular invasion within the resected specimen.

8.4.3   Follow-up

After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A)**.[Rec 8.18] After removal of a low-risk pT1 cancer, many endoscopists consider the surveillance policy employed for high-risk adenomas to be appropriate follow-up (see Ch. 9, Sect. 9.5.1, Rec. 9.16) **(III - B)**.[Rec 8.18] In the case of removal of a high-risk pT1 cancer without additional completion surgery for whatever reason, a more intensive programme of follow-up would be appropriate because of the increased risk of cancer recurrence. It is suggested that such patients benefit from quarterly endoscopic inspection of the polypectomy site for 1 year and then bi-annual inspection for a further 2 years. After this, the surveillance protocol for high-risk adenomas can be adopted. Given the increased risk of extramural recurrence in patients with high-risk pT1 cancers without completion surgery, it is

also appropriate to use cross-sectional imaging of the abdomen on a bi-annual basis for a period of 3 years.

8.4.4 Synopsis

Summary of evidence

- When invasive cancer is present in a polypectomy specimen, the risk of residual disease is associated with distance from the resection margin, degree of differentiation and degree of lymphovascular invasion **(III).**

- The precise site of a polyp within the colon is difficult to define at colonoscopy **(VI).**

Recommendations for management of pT1 cancers

- If there is clinical suspicion of a pT1 cancer a site of excision should be marked with sub-mucosal India ink **(VI - C).**[Rec 8.16]

- Where a pT1 cancer is considered high-risk for residual disease, consideration should be given to completion colectomy along with radical lymphadenectomy, for both rectal cancer **(II - A)** and colon cancer **(VI - A).**[Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7, Sect. 7.5.3 and Rec. 7.7) **(III - A).**[Rec 8.17]

- After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9, Sect. 9.5.1, Rec. 9.16) **(III - B).**[Rec 8.18]

8.5 Management of colon cancer

The management of screen-detected colon cancer is not materially different from that of the management of symptomatic cancer. Management of pT1 colon cancer has been dealt with in Section 8.4. The following summary deals with management of colon cancer which is not limited to the submucosa; it is derived from evidence based guidelines (SIGN 2003; Otchy et al. 2004; Schmiegel et al. 2005; Labianca et al. 2010; NCCN 2010a).

8.5.1 Preoperative staging

Once the diagnosis of colon cancer has been made (usually by means of colonoscopic biopsy) it is essential to a) ensure that the whole colon has been visualised for second primaries or adenomas and b) screen the patient for metastatic disease.

The reason for visualising the whole colon is that 5% of patients with a colorectal cancer will have a synchronous cancer, and more will have adenomas that require removal.

If a complete colonoscopy has not yet been performed, either because the primary lesion precluded total colonoscopy or any other reason, the rest of the colorectum should be visualised radiologically

before surgery, if at all possible. This should be performed ideally by CT colography, or if this is not available, by high quality double contrast barium enema. If for any reason the entire colon is not visualised prior to surgery then a complete colonoscopy should be carried out within 3 to 6 months of excision of the colon cancer **(VI - B).**[Rec 8.19]

In terms of screening for metastatic disease, patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**[Rec 8.20]

8.5.2 Surgery

As with all patients with colon cancer, the quality of surgery for screen-detected cancers is central to the outcome. Safe, high-quality surgery is essential for screen-detected cancers given that surgery-related mortality will result in greater shortening of life for patients with screen-detected cancers compared with those with symptomatic cancers.

The exact nature of the colectomy will of course depend on the anatomical location of the tumour but in general terms the most common operations will be a right hemicolectomy for tumours in the caecum or ascending colon, an extended right hemicolectomy for tumours in the transverse colon up to the splenic flexure, a left hemicolectomy for tumours between the splenic flexure and the sigmoid colon and a sigmoid colectomy for tumours of the sigmoid colon.

There is accumulating evidence that radicality of surgery is associated with better long-term outcomes and it is recommended that all of these operations be carried out with a full lymphadenectomy that involves flush ligation of the feeding vessels at the superior mesenteric artery or aorta as appropriate (West et al. 2008b). There is also increasing evidence that outcomes after surgery for colon cancer, both short- and long-term, are dependent on the degree of specialisation and experience of the surgeon (McArdle & Hole 2004). Thus patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**[Rec 8.21]

Increasingly, laparoscopic surgery is being used to treat colon cancer, and screen-detected colon cancer is often amenable to this approach. The evidence suggests that advantages of laparoscopic surgery are related to short-term rather than long-term outcomes, but randomised controlled trials indicate that it is oncologically safe (Kuhry et al. 2008). Thus where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**[Rec 8.22] However, it is essential that if laparoscopic surgery is employed, the oncological principles outlined above are adopted. It is also essential that the surgeons carrying out laparoscopic surgery be fully trained in this technique.

8.5.3 Synopsis

Summary of evidence

- High-quality surgery is the optimal primary treatment for colon cancer **(III).**

- In appropriately selected patients laparoscopic colon cancer surgery can offer better short-term outcomes **(I).**

Recommendations for management of colon cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the

colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of colectomy **(VI - B).**[Rec 8.19]

- Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**[Rec 8.20]

- Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**[Rec 8.21]

- Where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**[Rec 8.22]

8.6 Management of rectal cancer

The management of screen-detected rectal cancer is not materially different from that of the management of symptomatic rectal cancer. Management of pT1 rectal cancer has been dealt with in Section 8.4. The following summary deals with management of rectal cancer which is not limited to the submucosa; it is derived from evidence based guidelines (SIGN 2003; Schmiegel et al. 2005; Tjandra et al. 2005; Glimelius, Pahlman & Cervantes 2010; NCCN 2010b). However, the issue of how to treat small rectal cancers that are technically suitable for local excision is particularly germane to screen-detected disease, and particular emphasis is placed on this area.

8.6.1 Pre-operative staging

Pre-operative staging considerations are the same as those for colon cancer, including visualisation of the entire colon, (see Section 8.5.1 and Recommendations 8.19 and 8.20).[Rec 8.23; 8.24] In addition, however, it is important that the primary tumour be imaged in order to assess the need for neoadjuvant therapy. It is recommended that MRI of the pelvis be carried out for this purpose **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C).**[Rec 8.25] It should also be borne in mind that large rectal adenomas may harbour invasive malignancy, and it is recommended that all of these should be evaluated pre-operatively by transrectal ultrasound in order to assess the likelihood of possible invasive malignancy. Endoscopic ultrasound may also be helpful in distinguishing T1 from T2 tumours.

8.6.2 Neoadjuvant therapy

For many years it has been recognised that adjuvant radiotherapy given either pre-operatively or post operatively reduces the risk of local recurrence after radical excision of rectal cancer. There is now good evidence that pre-operative treatment is superior to post-operative treatment (SIGN 2003; NCCN 2010b) and it follows that all patients with rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative radiotherapy with or without concomitant chemotherapy **(I - A).**[Rec 8.28] It is not possible to be

prescriptive regarding the regime as this is dependant on pre-operative assessment of the individual tumour, the fitness of the patient (particularly with regard to chemotherapy), and on local protocols.

8.6.3   Surgery

Radical surgery for rectal cancer consists of either anterior resection or abdomino-perineal excision of the rectum. The latter operation is reserved for tumours where it is impossible to mobilise the tumours sufficiently to achieve an anastomosis, and in specialist practice this accounts for less than 40% of all rectal cancers.

The main principle of rectal cancer surgery is to obtain an adequate circumferential margin clearance of the tumour and to this end all rectal cancers treated by radical surgery are best served by the technique of mesorectal excision **(II - A).**[Rec 8.26] In cancers of the upper rectum it is acceptable to transect the mesorectum 50 mm distal to the tumour, but in cancers of the lower two thirds, total mesorectal excision is required. Evidence is accumulating that when an abdomino-perineal excision is carried out, wide excision of the pelvic floor is required to obtain adequate tumour clearance (West et al. 2008a).

There is now very good evidence that the quality of the surgery is strongly correlated with local recurrence and survival (Quirke et al. 2009), and, as with colon cancer, both short- and long-term outcomes are dependent on the degree of specialisation and experience of the surgeon (McArdle & Hole 2004). Therefore all patients undergoing radical surgery for rectal cancer should have mesorectal excision by an adequately trained specialist surgeon **(VI - A).**[Rect 8.26]

The same general considerations regarding laparoscopic surgery for colon cancer apply to rectal cancer (see Sect. 8.5.2 and Rec. 8.22) **(I - B).**[Rec 8.27] It should be considered, however, that a recent Cochrane Review concluded that laparoscopic surgery for the upper rectum is feasible, but more randomised trials are required to assess the long-term outcome (Kuhry et al. 2008).

8.6.4   Post-operative radiotherapy

Post-operative radiotherapy plus concomitant chemotherapy is indicated when a rectal tumour has been removed without pre-operative radiotherapy and where the resection margins are threatened by invasive cancer (Sengupta & Tjandra 2001; Min et al. 2007; Park et al. 2008) **(III)**.

8.6.5   Management of small rectal cancers

A major effect of a screening programme is to increase the number of small primary cancers that are diagnosed, and because the rectum can be accessed transanally this opens up the possibility of local excision for small rectal cancers. This can be achieved using conventional approaches with specifically designed retractors (e.g. the Pratt Biovalve Retractor and the Lone Star Retractor) or, if the tumour is in the mid- or upper rectum, using transanal endoscopic microsurgery (TEM) (Tytherleigh, Warren & Mortensen 2008). If a decision is made to locally excise a proven rectal cancer, this must be done along with an underlying full-thickness disk of rectal muscle and a margin of normal tissue of at least 5 mm in order to maximise the chance of complete excision. It must be recognised that this is only

suitable for posterior rectal tumours or low anterior rectal tumours. A full-thickness excision of a high anterior rectal tumour, particularly in a female, can result in perforation into the peritoneal cavity.

The main issue surrounding local excision of early rectal cancers is the risk of recurrence, and the evidence is such that most surgeons consider the risk of local recurrence after local excision to be considerably higher than that after radical rectal excision (Tytherleigh, Warren & Mortensen 2008). The risk of recurrence is dependent on the depth of invasion of the primary tumour, tumour diameter, lymphovascular invasion and degree of differentiation (Bach et al. 2009). T2 tumours are associated with at least a 20% risk of recurrence after local excision (You et al. 2007); T1 tumours are associated with a lesser risk of local recurrence, but again this is dependent on the depth of invasion. Kikuchi sm1 level tumours (superficial one third of the sub-mucosa) are associated with a negligible risk of local recurrence and can be safely treated by local excision (Kikuchi et al. 1995). Kikuchi level sm2 tumours (superficial two thirds of sub-mucosa) are associated with an 8% risk of local recurrence, and Kikuchi level sm3 tumours (full thickness involvement of the sub-mucosa) are associated with almost the same risk of local recurrence as T2 tumours. Thus under most circumstances radical surgery for sm2 and sm3 tumours is indicated. If a local excision is made and the pT stage is T1 sm3 or worse then radical excision should be carried out provided the patient is fit enough for radical surgery **(II - B)**.[Rec 8.32]

There is, however, a school of thought that local excision combined with radiotherapy plus or minus chemotherapy may produce acceptable local recurrence rates in T1, T2 and even T3 tumours; however the evidence to support this comes from relatively small case series. A recent review of the literature examined the use of pre-operative chemoradiation (CRT) and local excision, and found that local recurrence was 0% for those with pT0 tumours (i.e. complete response to CRT), 2% for pT1 tumours, 7% for pT2 tumours and 21% for pT3 tumours (Borschitz et al. 2008). (Note: in this context, pT refers to the *histopathological* T stage determined on the resection specimen after CRT).

There have been two RCTs comparing local excision by means of TEM and radical resection. One compared TEM alone with radical resection for T1 carcinoma (Winde et al. 1996), and the other compared TEM plus pre-operative CRT with radical surgery for T2 tumours (Lezoche et al. 2008). Both demonstrated significantly shortened operating times, less blood loss, less analgesic usage and shorter duration of hospitalisation with the TEM approach, but although neither demonstrated a difference in local recurrence rates, neither trial was sufficiently powered to examine this outcome.

In summary, with the exception of sm1 T1 cancers, there is a significant risk of local recurrence after local excision, although this may be modified by pre-operative CRT.

This view is supported by two recent systematic reviews (Middleton, Sutherland & Maddern 2005; Suppiah et al. 2008). Therefore, local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is fit for radical surgery **(III - B)**.[Rec 8.29] Furthermore, in patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C)**.[Rec 8.31]

If however there is doubt about the fitness of the patient for radical surgery, local excision of more advanced rectal cancer could be considered **(III - B)**.[Rec 8.30]

8.6.6 Synopsis

Summary of evidence

- The quality of surgery for rectal cancer, particularly with respect to circumferential margin involvement and the plane of surgery are strongly associated with outcome in terms of local recurrence and survival **(III)**.

- Although the evidence is not as extensive as for colon cancer, there is evidence that laparoscopic surgery for rectal cancer may be associated with better short-term outcomes without significant detriment **(I)**.

- Preoperative radiotherapy is associated with improved local recurrence rates and improved survival in appropriate patients undergoing radical surgery for rectal cancer **(I)**.

- Although small rectal cancers can be excised locally, local recurrence rates are higher than with radical surgery, with the exception of early (sm1) T1 cancers **(III)**.

- If a rectal cancer can be downstaged to pT0 or pT1 with CRT, local excision is associated with low local recurrence rates **(V)**.

Recommendations for management of rectal cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of excision of the rectal cancer **(VI - B)**.[Rec 8.23]

- Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI - B)**. Routine chest CT is not recommended **(III - D)**.[Rec 8.24]

- Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C)**.[Rec 8.25]

- All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II - A)** by an adequately trained specialist surgeon **(VI - A)**.[Rec 8.26]

- Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I - B)**.[Rec 8.27]

- All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I - A)**.[Rec 8.28]

- Local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is not fit for radical surgery **(III - B)**.[Rec 8.29]

- In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III - B)**.[Rec 8.30]

- In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C)**.[Rec 8.31] If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II - B)**.[Rec 8.32]

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

Colonoscopic surveillance following adenoma removal

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Guiding principles

1. Patients with previous adenomas are at increased risk for recurrent adenomas and thus eventually colorectal cancer. This risk is thought to depend on findings during baseline colonoscopy, in particular the number, size and histological grade of removed adenomas. This allows categorisation of patients into different risk groups. The indication and interval for surveillance is determined primarily by the presumed risk for recurrence of advanced adenomas and cancer, and secondarily also by age, co-morbidity, and patient wishes.

2. The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage.

3. Colonoscopy is a costly, invasive and scarce resource. Therefore colonoscopy surveillance should be undertaken only in those at increased risk and at a minimum frequency required to provide adequate protection against the development of cancer.

4. If colonoscopy surveillance is undertaken, it should be performed to the highest standard.

5. The surveillance strategy should be based on an assessment of the risk of developing advanced adenomas and colorectal cancer after a baseline colonoscopy.

6. Patients can be divided into low, intermediate and high risk groups, and the interval to the first follow-up examination can vary accordingly. A reassessment can be made based on findings at the first and subsequent follow-up examinations.

7. The risk stratification is predicated on an assumption that the initial and subsequent colonoscopies are of high quality and that there is complete removal of any detected lesions.

8. Surveillance colonoscopy consumes considerable endoscopic resources and may prevent a country that has difficulty meeting demand from sustaining reasonable waiting times. Screening programmes should have a policy on surveillance with a hierarchy of action for different risk groups based on resource availability.

Recommendations[1]

Risk stratification (see Figure 1)

9.1 Patients can be divided into low, intermediate and high risk groups with respect to their risk of developing advanced adenomas and cancer based on findings at baseline colonoscopy. The surveillance strategy can vary accordingly **(III - A)**.^{Sect 9.1; 9.3.1-3}

9.2 A readjustment of the strategy can be made based on findings at the first and subsequent surveillance examinations **(III - C)**.^{Sect 9.1; 9.4.1}

9.3 **Low risk**. Patients with only one or two small (<10 mm) adenomas are at low risk, and should be returned to the screening programme **(III - A)**.^{Sect 9.3.1}

9.4 **Intermediate risk.*** Patients with three or four small adenomas or at least one adenoma of size ≥10 mm and <20 mm are at intermediate risk **(III - A)** and should be offered surveillance at 3-yearly intervals **(II - A)**. After one negative exam, the interval can be extended to 5 years **(V - C)**. After two consecutive normal exams, the patient can return to routine screening **(VI - C)**.^{Sect 9.3.2; 9.4.1}

* Some programmes may wish to include small (<10 mm) adenomas with a villous component or with high grade neoplasia[2] in this group **(III - C)**.^{Sect 9.2.2.3; 9.3.1}

9.5 **High risk.** If either of the following is detected at any single examination (at baseline or follow-up): 5 or more adenomas, or an adenoma ≥20 mm, the patient is at high risk and an extra examination should be undertaken within 12 months, to check for missed synchronous lesions, before initiating 3-yearly surveillance **(III - B).** After two consecutive normal exams, the interval can be extended to 5-yearly **(V - C).** In the absence of evidence on the safety of stopping surveillance in the high risk group, surveillance should continue, taking into account Recommendations 9.10 and 9.11 **(VI - C)**.^{Sect 9.3.3; 9.4.1}

Quality of colonoscopy and removal of colorectal lesions

9.6 The risk stratification is based on accurate detection and complete removal of adenomas otherwise risk status will be underestimated **(III - A)**.^{Sect 9.1; 9.2.1.1}

9.7 Exams should be performed only after adequate bowel preparation i.e. without any residual stool or liquid in the lumen that could mask any suspicious area (see also Ch. 5, Rec. 5.22) **(VI – A)**. Exams should be complete to the caecum and there should be slow, careful inspection of the colonic mucosa during withdrawal of the scope (See Ch. 5, Rec. 5.35) **(I - A)**.^{Sect 9.2.1.1; 5.3.3; 5.4.5.1}

9.8 Patients with a failed colonoscopy should, if possible, undergo repeat colonoscopy or an alternative complete colonic examination, particularly if they are in the high risk group **(VI - B)**.^{Sect 9.2.1.2}

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.

[2] For consistency between the chapters of the European Guidelines, size and histopathology of endoscopically removed colorectal lesions are described using the scale (*mm*) and terminology (*neoplasia* rather than *dysplasia*) as recommended in Chapter 7 *Quality assurance in pathology in colorectal cancer screening and diagnosis*. This terminology is used in the Guidelines even though *cm* and *dysplasia* are used to report size and histopathology in other publications.

Figure 9.1: Recommended surveillance following adenoma removal. (For explanation see Recommendations 9.1–9.20 and Sections 9.3–9.5)

COLONOSCOPIC SURVEILLANCE FOLLOWING ADENOMA REMOVAL (EU 2010)

Baseline colonoscopy (CS)[1]

Low risk
1-2 adenomas
AND
both small (<10 mm)

AND tubular AND low grade neoplasia[2]

A

Routine Screening[3]

Intermediate risk
3-4 small adenomas
OR
at least 1 ≥10 mm/<20mm

OR villous OR high grade neoplasia[2]

B

3 years

High risk
≥ 5 small adenomas
OR
At least one ≥20 mm

C

Within 1 year[4]

Findings at surveillance CS

- One negative exam → **5 yearly**
- Two consecutive negative exams → **Routine Screening[3]**
- Low or intermediate risk adenomas → **B**
- High risk adenomas → **C**

Findings at surveillance CS

- Negative, low or intermediate risk adenomas → **3 yearly**
- Two consecutive negative exams → **5 yearly**
- High risk adenomas → **C**

Notes:

[1] Baseline colonoscopy must be complete in order to accurately assess risk.

[2] Optional additional criteria

[3] Other consideration: age, family history, accuracy and completeness of examination

[4] Clearing colonoscopy to check for missed lesions

9.9   The site of large sessile lesions removed piecemeal should be re-examined at 2–3 months. Small areas of residual tissue can then be treated endoscopically, with a further check for complete eradication within 3 months. India ink tattooing aids recognition of the site of excision at follow-up. If extensive residual lesion is seen, surgical resection must be considered, or alternatively, referral to a colonoscopist with special expertise in advanced endoscopic excision. **(VI - B).**[Sect 9.2.1.3]

Stopping surveillance

9.10   The decision to undertake each colonoscopic surveillance examination should depend not only on adenoma characteristics, but also on the patient's age and wishes, and the presence of significant co-morbidity. The patient status should be established prior to attendance for each examination **(VI - A).**^{Sect 9.4.2}

9.11   The cut-off age for stopping surveillance is usually 75 years, but this should also depend upon patient wishes and co-morbidity **(VI - A).**^{Sect 9.4.2}

9.12   Following cessation of surveillance, individuals should be returned to the population screening programme **(VI - C).**^{Sect 9.4.2}

Family history

9.13   Recommendations should not differ for patients with a family history who are found to have adenomas, unless it is suspected that they have one of the dominantly inherited conditions. **(III - B).**^{Sect 9.2.3.2}

Symptoms

9.14   New symptoms should be assessed on the basis that a recent clearance colonoscopy reduces the chance of advanced adenomas and cancers but does not eliminate the risk altogether **(III - A).**^{Sect 9.4.3}

Role of faecal occult blood testing

9.15   The potential benefit of supplementing colonoscopy exams with faecal occult blood testing is presumed to be too small to warrant double testing; therefore it is recommended to stop faecal occult blood testing in individuals who are undergoing surveillance **(VI - C).**^{Sect 9.4.4}

Guideline following local removal of a pT1 cancer

9.16   By their nature locally removed pT1 cancers are high risk lesions and therefore should undergo a surveillance strategy similar to the high risk adenoma group **(III - B).**^{Sect 9.5.1}

Guideline following detection of serrated adenomas

9.17   For surveillance purposes, serrated adenomas (traditional serrated adenomas and mixed polyps with at least one adenomatous component) should be dealt with like any other adenoma; there are no data to suggest that different surveillance intervals are required **(VI - C).**^{Sect 9.5.2; 7.2; 7.2.4.4; 7.2.4.5}

Guideline following detection of hyperplastic polyps or other non-neoplastic serrated lesions

9.18   There is no evidence that patients in whom only small, distally located hyperplastic polyps are detected are at increased risk for colorectal cancer; therefore they should be offered routine screening **(III - A).**^{Sect 9.5.3; 7.2.4.2}

9.19   One or more large (≥10 mm) hyperplastic polyps or other non-neoplastic serrated lesions anywhere in the colon or multiple smaller lesions of these types in the proximal colon may confer an increased risk, but there are no data available to indicate appropriate surveillance intervals **(VI - B).**^{Sect 9.5.3}

Quality improvement

9.20   Every screening programme should have a policy on surveillance. The policy may limit surveillance to the high risk group if sufficient resources are not available to include people with lower risk **(VI - B).**^{Sect 9.7}

9.21   The responsibility of programme management to assure the quality of screening services includes quality assurance of surveillance. For surveillance, the same principles, methods and

standards of quality assurance apply that are elucidated elsewhere in the first edition of the European Guidelines **(VI - B).**^{Sect 9.7} [Sect 9.7]

9.22   Adherence to the Guidelines should be monitored **(VI - A).**[Sect 9.7.1]

9.23   Surveillance histories should be documented and the results should be available for quality assurance **(VI - A).**[Sect 9.7.2]

9.24   The occurrence of colorectal cancer in any individual in whom adenomas or pT1 cancers have been detected at a previous exam should be captured as an auditable outcome for any surveillance programme **(VI - B).**[Sect 9.7.3]

9.1 Introduction

The adenoma is the precursor of the vast majority of colorectal cancers and is the most frequently detected lesion when colonoscopy is performed, either as a primary screening test or for investigation of a positive stool test (Imperiale et al. 2000; Lieberman et al. 2000; Schoenfeld et al. 2005). Hyperplastic polyps are also frequently detected during endoscopic examinations, but most are of no clinical significance.

The previous chapter has dealt with the management of colorectal lesions detected during endoscopy: they are invariably removed for histopathological assessment unless they are smaller than 3 mm and located in the distal rectum, and therefore likely to be innocuous hyperplastic polyps.

This chapter deals with decisions about the need for subsequent surveillance after removal of colorectal lesions once a pathological diagnosis has been made. The main focus of the chapter is on surveillance following adenoma removal but a small section has been devoted to other types of lesions including locally-removed pT1 cancers, serrated adenomas, hyperplastic polyps and other non-neoplastic serrated lesions.

Following initial detection and removal of adenomas, one third to one half of people will be found to have further adenomas within 3 years. In addition, cancer is detected in 0.3–0.9% within 5 years in patients undergoing surveillance (Nozaki et al. 1997; Alberts et al. 2000; Schatzkin et al. 2000; Lund et al. 2001; Baron et al. 2003; Robertson et al. 2005; Arber et al. 2006; Baron et al. 2006; Bertagnolli et al. 2006; Martinez et al. 2009). Many of these adenomas and cancers represent lesions missed at baseline colonoscopy, emphasising the importance of high quality examinations (Rex et al. 2002).

One of the primary purposes of colonoscopic surveillance is to prevent the development of colorectal cancer by removing new or missed adenomas before they have had a chance to progress to malignancy. Not all cancers are prevented by colonoscopy (Bressler et al. 2004; Robertson et al. 2005). Thus surveillance also aims to detect cancer at an earlier stage to increase the chance of survival.

Colonoscopy, with or without removal of a lesion, is an invasive procedure with a small but not insignificant risk of major complication, either from perforation (2% with, and 0.06% without excision), or from major post-excision haemorrhage (0.2%–2.7%, depending on size of lesion) (Macrae, Tan & Williams 1983; Nivatvongs 1986; Waye, Lewis & Yessayan 1992; Rosen et al. 1993). Surveillance colonoscopies also place an important burden on endoscopy services. In the USA, 22% of all colonoscopies in patients over 55 years are performed for surveillance purposes (Lieberman et al. 2005). For these reasons, surveillance colonoscopy should be targeted at those who are most likely to benefit, and at the minimum frequency required to provide adequate protection against the development of cancer.

The malignant potential of an adenoma - that is the chance that it harbours a focus of invasive cancer, or that it would progress to malignancy if not removed - varies according to its size, histology and grade of neoplasia (Muto, Bussey & Morson 1975; Eide 1986). Adenomas that are 10 mm or larger, have a villous component, or contain areas of high grade neoplasia have a higher malignant potential and are frequently described as "advanced"; however some studies, including the US National Polyp Study, include only large size (>10 mm) and high grade neoplasia in this definition (Winawer et al. 1993) (see Ch. 7, Sect. 7.2, 7.2.2, 7.3, and 7.3.2).

The future risk of diagnosing cancer or advanced adenomas following adenoma removal depends primarily on two major factors: the quality of the baseline colonoscopy and the characteristics of previously removed adenomas.

These Guidelines provide evidence that patients can be divided into low, intermediate, and high risk groups based on findings at baseline colonoscopy, and that the surveillance strategy can vary accordingly (see Figure 1 and Sections 9.3.1-3) **(III - A).**[Rec 9.1] The Guidelines also provide limited evidence that readjustment of the strategy can be made based on findings at the first and subsequent surveillance examinations (see Section 9.4.1) **(III - B).**[Rec 9.2]

9.2 Risk factors for advanced adenomas and cancer after baseline removal of adenomas

9.2.1 Procedural factors

9.2.1.1 Quality of colonoscopy

The efficacy and safety of the Guidelines in reducing risk of colorectal cancer depends on accurate detection and removal of baseline adenomas; otherwise risk status will be underestimated (see also Section 9.1) **(III - A).**[Rec 9.6]

Colonoscopy is not 100% sensitive even when intubation to the caecum is achieved. Adenomas, advanced adenomas and cancers can be missed, particularly by endoscopists using poor technique (Rex 2000). Miss rates for small adenomas at back-to-back colonoscopies are approximately 25%–50% (Hixson et al. 1990; Rex et al. 1997a; Heresbach et al. 2008), but the significance of this is as yet unclear. Of more concern is the observation that up to 6% of larger adenomas (≥10 mm) (Rex et al. 1997a; Bensen et al. 1999; Heresbach et al. 2008) and around 4% of cancers are missed at colonoscopy (Bressler et al. 2004; Farrar et al. 2006). These figures are remarkably similar to the detection rates of adenomas and advanced adenomas at first follow-up, suggesting that the majority of lesions detected at early follow-up were missed at baseline.

The risk stratification for surveillance is based partly on the assumption that patients with multiple or advanced adenomas are more likely to develop new important lesions. However, it also considers that these same subjects are more likely to harbour missed lesions that require early follow-up endoscopy. High quality baseline colonoscopy with adequate full assessment of the colon and complete removal of all adenomas is therefore essential and might have a similar magnitude of effect on colorectal cancer incidence as intensifying surveillance in most patients.

If colonoscopy surveillance is undertaken, it should also be done to the highest standard (Rex et al. 2002) (Chapter 5, Section 5.1.2). Most interval cancers in people undergoing surveillance are lesions that were missed or incompletely removed at the previous colonoscopy (Pabby et al. 2005; Robertson et al. 2005).

Infrequent high quality exams are probably more effective in preventing colorectal cancer than are frequent low quality exams.

Exams should be performed only after adequate bowel preparation i.e. without any residual stool or liquid in the lumen that could mask any suspicious area (see also Ch. 5, Rec. 5.22) **(VI – A)**. Exams should be complete to the caecum and there should be slow, careful inspection of the colonic mucosa during withdrawal of the scope (see Ch. 5, Rec. 5.35) **(I - A).**[Rec 9.7]

Higher detection rates are associated with adequate distension, suction and cleaning, position change, and slow and meticulous examination of the colonic mucosa, including behind folds (see also Chapter 5, Section 5.3.3 and 5.4.5.1).

When a small polyp is detected during insertion it is frequently difficult to relocate it on withdrawal. Where possible, consideration should be given to removing *small* lesions immediately on detection. Scanning the colonic mucosa during both insertion and withdrawal allows for essentially two examinations and potentially a reduction in the miss rate of small lesions. Removing larger lesions on insertion is not generally advisable because of the increased risk of bleeding and a possible increased risk of perforation.

9.2.1.2 Incomplete or inadequate colonoscopy

Patients with a failed colonoscopy should, if possible, undergo repeat colonoscopy or an alternative complete colonic examination, particularly if they are in the high risk group **(VI - B).**[Rec 9.8]

The decision may depend on patient factors such as age, risk group, the findings at the current examination, the difficulty of the examination, and the potential risks of repeating it, along with the general health and concerns of the patient. It also depends on local factors, such as waiting lists and whether the examination could be performed by a more experienced endoscopist.

In the US National Polyp Study (NPS), the examination was repeated if the baseline colonoscopy did not clear the colon with high confidence. Repeat examinations were required in 13% of exams (Winawer et al. 1993). The NPS authors attribute the low subsequent risk of cancer seen in the NPS cohort compared with other studies (Pabby et al. 2005; Robertson et al. 2005; Farrar et al. 2006) in which cancers were detected early in the surveillance programme to be the result of the careful baseline clearing of adenomas.

9.2.1.3 Management of incomplete adenoma excision

The safety and efficacy of the Guidelines depend on the complete and safe removal of all adenomas detected at colonoscopy.

Incompletely removed, large, flat lesions pose a high risk of cancer. At least one quarter of all cancers diagnosed within 3 years of a complete colonoscopy develop at the site of a previous excision (Pabby et al. 2005; Lieberman et al. 2007).

The management of large, sessile lesions removed piecemeal, is described in Chapter 8, Section 8.3.6. The site of excision should be re-examined after 2–3 months. Small areas of residual tissue can then be treated endoscopically, with a further check for complete eradication within 3 months. India ink tattooing aids recognition of the site of excision at follow-up. If extensive residual lesion is seen, surgical resection must be considered, or, alternatively, referral to a colonoscopist with special expertise in advanced polypectomy **(VI - B).**[Rec 9.9]

9.2.2 Characteristics of baseline adenomas

9.2.2.1 Number of adenomas

Multiplicity of adenomas is the most consistent predictor of the detection of advanced pathology or cancer at follow-up.

In a meta-analysis of several colonoscopic surveillance studies (Saini, Kim & Schoenfeld 2006), patients with 3 or more adenomas at baseline were at an approximately two-fold increased risk of advanced neoplasia during surveillance compared with those with only 1–2 adenomas. In a more recent pooled analysis (Martinez et al. 2009) that included eight US studies with a combined population of 9167 men and women with previously removed colorectal adenomas, advanced adenomas were detected at follow-up within 5 years in 12% (n=1082) and cancer in 0.6% (n=58). There was a highly significant linear trend of increasing frequency of advanced neoplasia (advanced adenomas and cancers) with increasing number of baseline adenomas detected. Compared with having a single baseline adenoma, risk was increased twofold in those with 3–4 adenomas and was increased fourfold in those with 5 or more adenomas. Another prospective study not included in the above analyses also confirmed these results (Cafferty et al. 2007).

The high detection rate of advanced neoplasia at follow-up after removal of multiple adenomas might result from a higher miss rate combined with a potential for such adenomas to be more advanced.

9.2.2.2 Size of adenomas

In several (Saini, Kim & Schoenfeld 2006; Martinez et al. 2009) but not all observational studies (Van Stolk et al. 1998), increased adenoma size has been found to predict detection of advanced adenomas and cancer at follow-up. In the recent large US pooled study (Martinez et al. 2009), risk was increased twofold for individuals who had at least one adenoma of size 10–<20 mm and threefold for size ≥20 mm, compared with those who only had adenomas <10 mm.

One reason for the inconsistent reporting of adenoma size as a risk factor for advanced adenoma recurrence is that current guidelines use 1 cm as a cut-off for identifying patients at higher risk and there are shorter intervals between surveillance exams for such patients in many studies, thereby attenuating risk. There are also inaccuracies in the endoscopic assessment of the size of adenomas, particularly around the 1 cm threshold (Morales et al. 1996; Schoen, Gerber & Margulies 1997), with frequent rounding up to 1 cm.

It is recommended that all measurements are reported in mm. When present, the pathologist's size should be used. If this is absent or if the lesion is fragmented, then the endoscopy size should be used (see Ch 7, Rec. 7.8 and 7.9, Sect. 7.2.1, 7.6.2 and 7.6.3).

9.2.2.3 Adenoma histology

The presence of tubulovillous or villous histology in a baseline adenoma is an inconsistent predictor of advanced neoplasia at subsequent surveillance colonoscopy. Correlations between size and histology of adenomas mean that the effects of the two factors are difficult to separate (Lieberman et al. 2008). Furthermore, sampling errors in small biopsies and large lesions exacerbate difficulties in interpretation, and classification of adenoma histology is subjective and prone to wide inter-observer variability (Costantini et al. 2003).

In a meta-analysis and systematic review (Saini, Kim & Schoenfeld 2006) on baseline risk factors for advanced adenomas, there was no significant difference between tubulovillous or villous vs. tubular adenomas in any of the individual studies. A subsequent prospective study found an increased risk of recurrence of villous adenomas among patients who had villous adenomas detected at baseline (Cafferty et al. 2007). However, in the large pooled US analysis (Martinez et al. 2009), the strong association between baseline villous histology (including tubulovillous and villous) seen in univariate analyses was almost completely attenuated in the multivariate analysis. Thus, considering that adenoma characteristics such as number and size represent stronger predictors of developing advanced pathology, and taking into account the low reproducibility of the histology classification, histology alone may not be considered a significant risk factor for neoplasia recurrence.

9.2.2.4 Grade of neoplasia[3]

Most studies compare risks for the subsequent development of advanced adenomas according to whether there are baseline adenomas with high grade dysplasia. This corresponds to high grade neoplasia as described in Chapter 7 in Section 7.3.2 and Table 7.1. Some individual studies (Bonithon-Kopp et al. 2004; Lieberman et al. 2007) have found risk to be higher in patients with high grade dysplasia in adenomas of any size. Similar results were reported by one meta-analysis (Saini, Kim & Schoenfeld 2006), although it included only two studies that evaluated the role of grade of neoplasia. The association was not confirmed, however in a large pooled analysis using individual-level data, in which neoplasia data were available from 6 studies, after adjusting for several risk factors (Martinez et al. 2009). Thus, available evidence suggests that high grade neoplasia may not have independent predictive value for the detection of advanced colorectal adenomas and cancer, and that after removal of small adenomas with high grade neoplasia, the risk of developing further advanced adenomas and cancer is not increased. Caution should be exercised with this interpretation of the evidence since high grade neoplasia is present in only 1% of adenomas smaller than 10 mm (Lieberman et al. 2008); therefore most studies suffer from small numbers and a lack of statistical power. It is therefore reasonable to be pragmatic and decide locally about whether to offer surveillance to individuals with small (<10 mm) adenomas demonstrating high grade neoplasia **(III - C).**[Rec 9.4]

9.2.2.5 Location

Several studies have found that having any proximal adenoma at baseline significantly increases risk for subsequent advanced neoplasia. Risks in individual studies vary from 1.5 to 2.5 fold compared with having adenomas only in the distal colon (Baron et al. 1995; Greenberg et al. 1994; Alberts et al. 2000; Alberts et al. 2005; Saini, Kim & Schoenfeld 2006; Laiyemo et al. 2009; Martinez et al. 2009).

It is as yet unclear how the finding of proximal adenomas should influence the Guidelines.

9.2.3 Patient characteristics

9.2.3.1 Age and sex

Older age has been found to be associated with an increased risk of advanced neoplasia in several studies (Yamaji et al. 2004; Martinez et al. 2009).

It is possible that the higher risk with older age is related to the increased difficulty of performing an accurate examination. Combined with a greater likelihood of older people having an advanced lesion, there is a greater chance of missing advanced neoplasia at older ages.

However, advanced age is not an indication for more intense surveillance. Colonoscopy is likely to be less successful and more risky at older ages. Furthermore, the lead time for progression of an adenoma to cancer is around 10 to 20 years, which is of the same order as the average life-expectancy of an individual aged 75 years or older, suggesting that most will not benefit from surveillance.

Male sex has been shown to be a moderate risk factor in some (Martinez et al. 2009) but not all studies (Yamaji et al. 2004). However, it is unclear how this finding should affect Guidelines.

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[3] See Footnote 2 in this chapter (p. 276).

9.2.3.2 Family history

Several studies have found that the prevalence of adenomas on baseline colonoscopy is increased in patients with a family history of colorectal cancer (Bonelli et al. 1988; Cannon-Albright et al. 1988; Pariente et al. 1998; Lieberman et al. 2000). Other studies have suggested that patients with a family history also have an increased risk of advanced or multiple adenomas (Neklason et al. 2008; Wark et al. 2009).

The US National Polyp Study (Zauber et al. 1999) found that the subsequent risk of developing advanced adenomas in people undergoing surveillance was increased in people aged ≥60 years who had a parent affected by colorectal cancer. However, these data are published only in abstract form. One other study (Nusko et al. 2002) found that having a parent with a history of colorectal cancer conferred an increased risk, but this was based on small numbers, and other studies have not confirmed this finding. Detection rates of advanced adenomas among 1287 participants in a trial of wheat bran fibre were unaffected by inclusion of family history in a multivariate model after adjustment for adenoma characteristics at baseline (Martinez et al. 2001). Similarly, in the recent US pooled analysis, the risk of developing advanced neoplasia during surveillance was not influenced by family history (Martinez et al. 2009).

Thus there is no consistent evidence to suggest that recommendations on adenoma surveillance should differ for patients with a family history, unless it is suspected that they have one of the dominantly inherited conditions **(III - B).**[Rec 9.13]

9.3 Risk groups and surveillance intervals

Recommendations from several European countries and the USA have defined three risk groups: low, intermediate and high risk for the development of colorectal cancer and advanced adenomas, based on the number and characteristics of adenomas detected at baseline colonoscopy (Hoff et al. 1996; Atkin & Saunders 2002; Bjork et al. 2003; Winawer et al. 2006; Schmiegel et al. 2008). Stratifying patients with adenomas and adjusting intervals between exams can theoretically reduce the number of unnecessary procedures and thereby the burden and costs as well as the complication rate associated with adenoma surveillance, whilst protecting those at highest risk (see Figure 1 and Sections 9.3.1–3, 9.4 and 9.5).

Recommendations for surveillance intervals are based primarily on early trials and cohort studies. Because of the high recurrence rate of adenomas within 3 years after a baseline clearing examination, it was customary in the past to perform very frequent exams (even annually) (Ransohoff, Lang & Kuo 1991). The US National Polyp Study (Winawer et al. 1993) was a randomised comparison of two different surveillance intervals in 1418 patients with newly diagnosed adenomas removed at colonoscopy. In this study, the cumulative detection rate of advanced adenomas or cancer was 3% at 3 years, irrespective of whether 1 or 2 examinations were performed within the 3 year period. The Funen Adenoma Follow-up Study (Kronborg et al. 2006) was another randomised comparison of surveillance intervals. This study found that the incidence of advanced neoplasia was higher in patients examined at 4 compared with 2 years (8.6% vs. 5.2%), although the difference was not significant. However, on balance, the authors concluded that the more than 50% reduction in the number of examinations and the probable reduction in complications justified the longer interval.

These results suggested that the first follow-up colonoscopy should be delayed until at least 3 years after baseline polypectomy for most patients with adenomas. However, the data from these trials do not preclude the possibility that much longer intervals might offer adequate protection for most patients.

A long-term follow-up study of patients from St Mark's (Atkin, Morson & Cuzick 1992) showed that a proportion of patients with adenomas were at particularly low risk of developing colorectal cancer and may require no surveillance. Conversely, more recent studies (Martinez et al. 2009) have shown that 3-yearly screening may not be adequate to protect a small minority of patients who are at high risk of both advanced adenomas and cancer.

9.3.1 Low risk group

Five studies (Van Stolk et al. 1998; Zauber et al. 1999; Noshirwani et al. 2000; Martinez et al. 2001; Lieberman et al. 2007) in patients undergoing surveillance colonoscopies have identified a low risk group. All but one (Martinez et al. 2001) of these studies agreed that having only 1–2 adenomas confers a low risk of subsequent advanced adenomas, but disagreed on the importance of size and histology. As described in Section 9.2.2.3, size and histology are highly correlated and it is difficult to separate the effects of each variable.

The Veterans Affairs colonoscopy screening follow-up study in the USA (Lieberman et al. 2007) was the only study to have compared risk in people with low risk adenomas and those in whom no neoplasia was detected. They found that the cumulative risk of detecting advanced neoplasia at colonoscopy undertaken within 5 years in people with 1–2 small tubular adenomas was not significantly different from those with no neoplasia detected. However, the study was underpowered to observe any difference that might exist because there was poor attendance at follow-up among the no neoplasia group.

The longer term risk of developing colorectal cancer has been examined for patients from whom adenomas were removed from the distal sigmoid colon and rectum by sigmoidoscopy. No increased incidence of cancer was observed in comparison with the general population in 751 residents of Rochester, Minnesota, following removal of small (≤10 mm) colorectal polyps (Spencer et al. 1984), most of which were unexamined histologically. A similar study from St Mark's Hospital (Atkin, Morson & Cuzick 1992), in which all removed lesions were examined histologically, found that patients from whom only small (<10 mm) tubular adenomas were removed from the distal sigmoid colon or rectum had no long-term increased risk of developing colon cancer in comparison with the general population. Risk of rectal cancer was profoundly decreased compared with the unexamined population.

The US National Polyp Study found that the cumulative risk of colorectal cancer at 6 years following baseline colonoscopic removal of adenomas was 75% lower than the US population (Winawer et al. 1993). This study identified a higher risk group which included patients with multiple (≥3) or large adenomas (Weston & Campbell 1995), further emphasising the low risk among those with 1–2 small adenomas.

Thus it appears that whether the outcome is an advanced adenoma or cancer, future risk is low among patients with one to two small adenomas, whether or not histology is considered.

The benefits of surveillance colonoscopy are likely to be low in patients with 1–2 small adenomas and probably not cost-effective (Ransohoff, Lang & Kuo 1991). We recommend routine screening for this group **(III - A).**[Rec 9.3]

Some programmes may wish to include small (<10 mm) adenomas with a villous component or with high grade neoplasia in the intermediate risk group, although the available evidence is limited and inconsistent (see Section 9.2.2.3) **(III - C)**.[Rec 9.4]

9.3.2 Intermediate risk group

It has been shown consistently that patients with 3 or more adenomas are a higher risk group for the development of advanced adenomas and cancer, particularly if one of the adenomas is also large (≥10 mm) (Noshirwani et al. 2000; Martinez et al. 2009).

In the US National Polyp Study (Winawer et al. 1993), 9% of patients with 3 or more adenomas and 5% of those with a large adenoma removed at baseline developed an advanced adenoma by their first follow-up examination, compared with only 1% in those with a single adenoma. An analysis of 697 patients in the Cleveland Clinic Foundation Adenoma Registry (Noshirwani et al. 2000) showed that, compared with 1–2 small adenomas, risk is increased fivefold following removal of multiple (4 or more) small adenomas and tenfold following removal of multiple adenomas at least one of which is larger than 10 mm. In the pooled analysis of US studies, having 3–4 adenomas or an adenoma of size ≥10 mm was associated with an approximately twofold increased risk of advanced adenomas and cancer (Martinez et al. 2009).

There have been two studies of the long-term risk of colorectal cancer following removal of large distal colorectal lesions. Risk was increased threefold (compared with the general population) in Rochester, Minnesota residents from whom large lesions (≥10 mm and mostly adenomas) were removed (Lotfi et al. 1986). While in the study from St Mark's Hospital (Atkin, Morson & Cuzick 1992), risk of colon cancer was increased fourfold following removal of large (≥10 mm) distal adenomas or those with a villous component and sevenfold if there were also multiple adenomas.

Therefore having 3 or more adenomas or an adenoma ≥10 mm confers an increased risk of advanced adenomas and cancer and suggests that colonoscopic surveillance is warranted **(III - A)**. The results of the US National Polyp Study (Winawer et al. 1993) suggest that a 3-year interval to the first surveillance colonoscopy is adequate for most patients in this group **(II - A)**.[Rec 9.4]

There are few data to inform on intervals after the first examination (see Section 9.4).

9.3.3 High risk group

Recent studies have reported that a proportion of patients remain at increased risk of developing advanced neoplasia despite 3-yearly surveillance. In the pooled analysis of US studies (Martinez et al. 2009), having 5 or more adenomas conferred a fourfold increased risk, and having an adenoma of size ≥20 mm conferred a threefold increased risk. Missed and incompletely removed lesions may be an explanation for the high detection rate of advanced neoplasia (Pabby et al. 2005; Robertson et al. 2005; Farrar et al. 2006; Lieberman et al. 2007).

Thus, although not entirely consistent, the data suggest that an additional clearing colonoscopy at 12 months may be warranted in people found at a single colonoscopy to have 5 or more adenomas or an adenoma of size 20 mm or larger. These patients require careful surveillance colonoscopy because of the substantial risk of missing adenomas with high malignant potential **(III - B)**.[Rec 9.5]

The aim of a single early surveillance colonoscopy in this group is to remove synchronous lesions not detected at an examination at which ≥5 adenomas or at least one adenoma of size ≥20 mm is

removed. This complete colonoscopy examination should be distinguished from polypectomy site surveillance exams undertaken following piecemeal removal of sessile lesions (refer to 9.2.13).

9.4 Adjusting surveillance during follow-up

9.4.1 Significance of a normal surveillance colonoscopy

Khoury et al. (1996) undertook a retrospective examination of 389 patients who had undergone follow-up colonoscopy at 1-year intervals after resection of colorectal cancer. The adenoma detection rate at follow-up was 10% if the prior colonoscopy was negative and 40% if the prior colonoscopy was positive. If multiple adenomas were found at the prior examination, 70% of colonoscopies were positive. In another series (Blumberg et al. 2000), a normal follow-up colonoscopy was associated with a lower incidence of subsequent adenomas at the next colonoscopy compared with those with adenomas detected (15% vs. 40%).

None of the studies to date has provided evidence to inform Guidelines on the degree of protection afforded by a single negative follow-up examination in patients with intermediate or high risk adenomas at baseline. One study (Wegener, Borsch & Schmidt 1986) has shown that a negative result at first follow-up examination in patients with multiple adenomas initially does not preclude the subsequent development of new adenomas. Thus, until data to the contrary are available, it must be assumed that patients in the intermediate or high risk groups remain at increased risk despite a single negative follow-up examination. Following two consecutive negative examinations there can be greater confidence that adenomas have not been missed and that subsequent risk is therefore decreased.

Given the limited available evidence, we recommend extending the interval after the first negative surveillance colonoscopy to five years in the intermediate risk group **(V - C)**. For the high risk group, we recommend a 2-year extension of the interval after two consecutive negative surveillance colonoscopies **(V - C)**.

Following two complete, negative surveillance colonoscopies we assume that patients in the intermediate risk group are probably at low risk, and surveillance can cease **(VI - C)**.[Rec 9.4; 9.5]

In the absence of evidence on the safety of stopping surveillance in the high risk group we recommend continuing surveillance in this group, taking into account the issues discussed in the following section **(VI - C)**.[Rec 9.5]

9.4.2 Stopping surveillance

The risks and benefits of adenoma surveillance must be balanced at all ages, particularly in patients who have significant co-morbidity. The decision to undertake each colonoscopy examination at follow-up should depend not only on the number and type of adenomas, but also on the patient's age and wishes, and the presence of significant co-morbidity. Patient status should therefore be established prior to attendance for each examination **(VI - A)**.[Rec 9.10; 9.11]

Following cessation of surveillance, individuals of appropriate age should be returned to the population screening programme **(VI - C).**[Rec 9.12]

The cut-off age for stopping surveillance is usually 75 years, but this should also depend upon patient wishes, co-morbidity and findings at surveillance exams **(VI - A).**[Rec 9.11] Older patients should be advised that adenomas generally take many years to become malignant, and newly detected adenomas are likely to remain benign for the remaining lifespan of most people aged over 75 years. This should not preclude further surveillance in a fit and motivated individual who has a tendency to produce multiple or advanced adenomas at follow-up.

9.4.3   Symptoms developing between surveillance exams

New symptoms should be assessed on the basis that a recent colonoscopy reduces the chance of advanced adenomas and cancers but does not eliminate the risk altogether. (Winawer et al. 1993; Rex et al. 1997b; Brenner et al. 2006; Singh et al. 2006; Baxter et al. 2009; Martinez et al. 2009) **(III - A).**[Rec 9.14]

9.4.4   Role of faecal occult blood testing

The potential benefit of supplementing colonoscopy exams with faecal occult blood testing is presumed to be too small to warrant double testing; therefore it is recommended to stop faecal occult blood testing in individuals who are undergoing surveillance **(VI - C).** [Rec 9.15]

9.5   Colonoscopic surveillance guidelines following removal of other colorectal lesions

9.5.1   Locally removed pT1 cancers

There are two reasons for performing colonoscopic surveillance after local removal of a low risk pT1 cancer. One is to examine the remaining colon and rectum to detect intraluminal recurrence; the other is to detect metachronous cancer or adenomas (Rex et al. 2006).

By their nature polyp cancers are high risk lesions (Chu et al. 2003; Di Gregorio et al. 2005; Rex et al. 2006). They therefore should undergo a surveillance strategy similar to the high risk adenoma group **(III - B).**[Rec 9.16]

It is assumed that there has been a high quality baseline clearing examination to detect and remove all synchronous lesions. It is also assumed that the cancer has been completely removed and the site re-examined as described in Chapter 8, Section 8.4.

This policy should also apply to locally-removed pT1 cancers detected during surveillance exams in any risk group.

9.5.2 Serrated adenomas

For surveillance purposes, serrated adenomas (i.e., traditional serrated adenomas and mixed polyps with at least one adenomatous component; see Chapter 7, Section 7.2.4.4 and 7.2.4.5) should be dealt with like any other adenoma; there are no data to suggest that surveillance intervals different from those in Figure 1 are required **(VI - C).**[Rec 9.17]

9.5.3 Hyperplastic polyps and other non-neoplastic serrated lesions

There is evidence that patients in whom only small, distally located hyperplastic polyps are detected are not at increased risk for colorectal cancer. These patients should therefore be offered routine screening **(III - A).**[Rec 9.18]

Recent publications dealing with hyperplastic polyps and other serrated non-neoplastic lesions are limited by methodological issues such as small sample size and diagnostic accuracy (see also Ch. 7, Sect. 7.1 and 7.2.4). They therefore preclude risk analysis stratified by the size and location of these lesions (Imperiale et al. 2008; Li et al. 2009; Schreiner, Weiss & Lieberman 2010).

Patients found to have a large (≥10 mm) hyperplastic polyp or other non-neoplastic serrated lesion anywhere in the colon or multiple lesions of these types in the proximal colon may be at increased risk, but there are no data available to indicate appropriate surveillance intervals **(VI - B).**[Rec 9.19]

Hyperplastic polyposis was defined by Burt & Jass (2000) for the WHO Classification of Tumours as:

- at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 10 mm in diameter; or

- any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; or

- more than 30 hyperplastic polyps of any size distributed throughout the colon.

Studies have found an increased risk for colorectal cancer in patients with hyperplastic polyposis defined less stringently than the WHO criteria (Hyman, Anderson & Blasyk 2004; Boparai et al. 2010). However, the available information is insufficient to inform appropriate surveillance intervals in this group **(III - B).**[Rec 9.19]

9.6 Opportunity costs

Surveillance colonoscopy consumes considerable endoscopic resource and may, as a result, prevent a country from sustaining reasonable waiting times. This may adversely affect the symptomatic service and tarnish the reputation of screening. Thus a country may, as a result of limited endoscopic resources, choose to adopt the guidance for surveillance, but only of the high risk group until it has created the capacity to adopt the full guidance. The stratification of risk proposed by this, and most other guidelines on surveillance, enables a country to implement what it can afford (see Section 9.7).

9.7 Quality standards and auditable outcomes

The aim of this chapter on colonoscopic surveillance is to define the minimum requirements for protecting individuals in whom colorectal adenomas are detected at screening from subsequently developing fatal colorectal cancer. The degree of protection depends on the quality of colonoscopic examinations and the appropriate frequency of surveillance colonoscopies. Data on the effects of increasing intervals between exams is limited; however, these Guidelines are based on the best available evidence.

Every screening programme should have a policy on surveillance. The policy may limit surveillance to the high risk group, if sufficient resources are not available to include people at lower risk (see Section 9.6) **(VI - B).**[Rec 9.20]

The responsibility of programme management to assure the quality of screening services includes quality assurance of surveillance. For surveillance the same principles, methods and standards of quality assurance apply that are elucidated elsewhere in the first edition of the European Guidelines **(VI - B).**[Rec 9.21]

9.7.1 Adherence to the guideline

Adherence to the EU Surveillance Guidelines should protect patients from low quality exams and from inappropriately frequent or infrequent exams. Setting targets based on the Guidelines, monitoring performance, and acting on the results should help, among other things, to lower miss rates of important lesions at baseline. This, in turn, is likely to avoid misclassification of risk and to thereby improve surveillance results.

Adherence to the Guidelines should therefore be monitored **(VI - A).**[Rec 9.22]

Auditable outcomes:

- Percentage of people screened or already under surveillance who are assigned to the respective risk groups by the programme and the proportion of people allocated to each risk group who fulfil the Guidelines criteria for that group.

- In each risk group, the percentage in which the interval assigned in practice agrees with the interval recommended in the Guidelines.[4]

Patient choice and clinical factors should be removed from the denominator. The above data should be broken down and analysed by relevant subgroups, such as age, sex and region.

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[4] Not applicable to low risk category because persons with low risk are recommended to return to screening according to the EU Guidelines.

9.7.2   Timeliness of surveillance procedures

The programme should monitor whether the recommended surveillance procedures are happening and whether they are undertaken on time.

Therefore, surveillance histories should be documented and the results should be available for quality assurance **(VI - A).**[Rec 9. 23]

Auditable outcomes:

- Percentage of allocated procedures performed

- Of those that are performed, what percentage is performed within 6 months of the due date?

Patient choice and clinical factors should be removed from the denominator.

The above data should be broken down and analysed by relevant subgroups, such as risk category, age-group, sex and region.

9.7.3   Incident cancers

The occurrence of colorectal cancer in any individual in whom adenomas or pT1 cancers have been detected at a previous exam is a key auditable outcome for any surveillance programme **(VI - B).**[Rec 9.24]

Collecting this information will require linkage of data on the occurrence of cancer in the target population with the screening and surveillance histories of all people attending respective programmes.

The above data should be broken down and analysed by relevant subgroups, such as risk category, age-group, sex and region.

The data should also be subdivided into cancers detected at surveillance examinations; cancers diagnosed in the intervals between scheduled surveillance examinations; and cancers diagnosed after stopping surveillance (post surveillance cancers) which might inform on the safety of stopping surveillance in a specific patient.

Auditable outcomes in subgroups of individuals with histories of adenomas or pT1 cancers detected in screening or surveillance:

- Rate of cancers detected at a surveillance exam (surveillance detected cancers)

- Rate of cancers diagnosed before a scheduled surveillance exam (surveillance interval cancers)

- Rates of cancers diagnosed after stopping surveillance, and intervals to cancer diagnosis (post-surveillance cancers)

9.8 References

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

10

Communication

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Recommendations[1]

10.1 Developing communication strategies for an organised CRC screening programme is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening **(VI - A).**^{Sect 10.2.2.2}

10.2 Any framework developed to communicate CRC screening information must enable individuals to make an informed decision, and should be underpinned by the four ethical principles of autonomy, non-malfeasance, beneficence and justice **(VI - A).**^{Sect 10.2.2.2}

10.3 CRC screening programmes should provide balanced, quantified and unbiased information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risk factors). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation **(VI - A).**^{Sect 10.2.2.2}

10.4 CRC screening programmes should identify the barriers, needs and facilitators to informed decision-making (IDM) of their target population (including specific groups) **(VI - A)**. The information materials produced, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, and the intervention(s) used must conform to these identified information needs and facilitators. The public should be involved in the entire process, from identifying barriers, needs and facilitators to developing information materials **(VI - A).**^{Sect 10.2.2.2}

10.5 To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions **(VI - A).**^{Sect 10.2.2.2}

10.6 Primary health care providers should be involved in the process of conveying information to people invited for screening (see Ch. 2, Rec. 2.11) **(II - A).**^{Sect 10.4.1.1; 2.4.3.4; 2.4.3.4.1}

10.7 In the context of an organised programme, personal invitation letters, preferably signed by the GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation (see Ch. 2, Rec. 2.8) **(I - A).**^{Sect 10.4.1.2; 2.4.3.4.1, 2.4.3.2}

10.8 Although more effective than other modalities, phone reminders may not be cost-effective (see Ch. 2, Rec. 2.9) **(II - B).**^{Sect 10.4.1.2; 2.4.3.2}

10.9 Mailing of the FOBT kit may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics) as well as factors (such as the expected impact on participation rate) that might influence cost-effectiveness (see Ch. 2, Rec. 2.15) **(II - B).**^{Sect 10.4.1.3; 2.5.1.1}

10.10 Clear and simple instruction sheets should be provided with the kit (see Ch. 2, Rec. 2.16) **(V - A).**^{Sect 10.4.1.3; 2.5.1.1}

10.11 Use of a non-tailored leaflet for the general population is advised; the leaflet should be included with the invitation letter. Information about CRC screening risks and benefits, CRC risks (incidence and risks factor), meaning of test results, potential diagnostic tests and potential treatment options should be included **(VI - A)**. Illustrations may be used, which would be particularly useful for minorities, the elderly or low-literacy participants **(II - A).**^{Sect 10.4.2.1}

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[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

10.12 A tailored leaflet for "harder to reach" groups could be used if these groups can be identified **(II - B)**.^{Sect 10.4.2.1}

10.13 Although there is good evidence that leaflets can increase knowledge of CRC screening, there is inconclusive evidence on the impact of leaflets on informed decision making (IDM). As a consequence, other interventions should be used in addition to leaflets **(VI - A)**.^{Sect 10.4.2.1}

10.14 Video/DVD may be a useful component in a multi-modal intervention in addition to written information, and would be particularly useful for the elderly, minorities and low literacy participants **(I - B)**. For the elderly, increasing the number of components of the multi-modal intervention and the period over which these components are provided may be more effective **(I - B)**.^{Sect 10.4.2.2.1}

10.15 A computer-based decision aid could be used to help both the general population and specific groups to make informed decisions about CRC screening **(I - B)**. The computer-based decision aid should be "user-friendly" and designed to fit with the computer abilities of the target population (general or specific groups).^{Sect 10.4.2.2.2}

10.16 ICT-generated reminders[2] to physicians could be used as an opportunity to provide counselling to patients on CRC and CRC screening, if primary care or other health practitioners are involved, and if patient medical records are electronic and give screening status **(I - A)**.^{Sect 10.4.2.2.3}

10.17 If possible, all information provided by the screening programme should be available on a specific web site. This information should be regularly updated **(VI - A)**.^{Sect 10.4.2.2.4}

10.18 It is not cost-effective or feasible to implement a tailored reminder telephone call in the general population. It may be possible for CRC screening programmes to use such an intervention for "harder to reach" groups if these groups can be identified **(II - B)**. For example peer telephone support could be used.^{Sect 10.4.2.3.1}

10.19 Patient navigation could be used within CRC screening programmes, particularly to reach subgroups of the population such as the elderly, those with low literacy, and medically underserved patients. When used with minorities, the patient navigator should be from a similar ethnic background and/or live in the same community as the participant **(I - B)**.^{Sect 10.4.2.3.2}

10.20 Verbal face-to-face interventions with a nurse or physician could be used to improve knowledge and participation. They would be useful to reach subgroups of the population such as the elderly, minorities and those with low literacy **(I - A)**.^{Sect 10.4.2.3.3}

10.21 Nurses and primary care practitioners (GPs) should receive adequate training to be able to help people make informed decisions about CRC screening **(VI - A)**.^{Sect 10.4.2.3.3}

10.22 Community-based verbal face-to-face interventions such as church-based sessions or in-person interviews could be used to reach minorities, in the case where the providers of such interventions received adequate training **(II - B)**.^{Sect 10.4.2.3.3}

10.23 Mass media campaigns using celebrities may be used to increase the awareness of CRC and CRC screening programmes. However these should be complemented by other measures as the effects are only temporary **(V - C)**.^{Sect 10.4.2.4}

10.24 When addressed to minority groups, information provided by mass media campaigns should emphasise positive progress made by the minority group instead of emphasising racial disparities **(VI - C)**.^{Sect 10.4.2.4}

10.25 CRC screening programmes should work closely with advocacy groups and the media and provide them with up-to-date, accurate and comprehensive information about CRC and CRC screening **(VI - A)**.^{Sect 10.4.2.4; 10.4.2.5}

10.26 A telephone or ideally a verbal face-to-face intervention, e.g. nurse or physician intervention, should be used to inform a patient of a positive screening test result, as obtaining such a result

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[2] ICT-generated reminders are produced electronically using information and communication technologies.

could be a source of psychological distress for the patient. A letter informing the patient should not be used as the only way of notifying a positive result **(VI - A)**.^{Sect 10.4.3}

10.27 To increase endoscopy follow-up after a positive FOBT and facilitate communication, CRC screening programmes should, where possible:

- o Use a reminder-feedback and an educational outreach intervention targeted to the primary care physician **(II - A)**;

- o Provide patients with a written copy of their screening report **(II - A)**;

- o Facilitate patient consultation with a gastroenterologist **(V - B)**;

- o Describe the follow-up procedure, make the follow-up testing more convenient and accessible **(VI - A)**; and

- o Use direct contact intervention to address psychological distress and other specific barriers. **(V - B)**.^{Sect 10.4.3}

10.28 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see Ch. 5, Rec. 5.20) **(III - B)**.^{Sect 10.4.3; 5.3.2}

10.29 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see Ch. 5, Rec. 5.25) **(VI - B)**.^{Sect 10.4.3; 5.3.1}

10.30 Before leaving the endoscopy unit, patients should be informed about the outcome of their procedure and given written information that supports a verbal explanation (see Ch. 5, Rec. 5.26) **(VI - A)**.^{Sect 10.4.3; 5.5.3}

10.31 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see Ch. 5, Rec. 5.27) **(VI - B)**.^{Sect 10.4.3; 5.5.5}

10.32 Ideally, the invitation letter and the letter used for notification of a positive result should be sent with a leaflet and should encourage participants to read it **(VI - A)**.^{Sect 10.5.1}

10.33 Certain basic information, e.g. logistic/organisational information, description of the screening test, harms and benefits of screening, information about the FOBT kit and the bowel cleansing procedure, must be included in the invitation/result letter in case a person reads only the letter and not the leaflet **(VI - A)**.^{Sect 10.5.1}

10.34 Recommendations when FOBT is used for screening: FOBT invitation letter, FOBT invitation leaflet, FOBT result/follow-up letter, see Section 10.5.2.

10.35 Recommendations when FS or colonoscopy (CS) is used for screening, either as primary screening test (FS or CS) or to follow-up a positive FOBT result (only CS): Endoscopy invitation letter, Colonoscopy leaflet, Endoscopy result/follow-up letter, see Section 10.5.3.

10.1   Introduction

10.1.1   Using communication strategies for a colorectal cancer screening programme: goals and challenges

The essential goal of colorectal cancer (CRC) screening programmes is to reduce illness and death due to colorectal cancer. This requires the need to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend CRC screening. As adverse effects are intrinsic to screening practice, participants should understand that a balance exists between benefits and harms associated with CRC screening. In the policy brief *Screening in Europe*, Holland, Stewart & Masseria (2006) state that there is "above all, an imperative to involve participating individuals in decisions on screening and to give them clear and understandable information about what it involves". A key component of CRC screening programmes, therefore, is the information and education provided about CRC and CRC screening tests and procedures: people who use CRC screening services should receive accurate and accessible information that reflects the most current evidence about the CRC screening test and its potential contributions to reducing illness as well as information about its risks and limitations.

Providing effective information is particularly challenging in CRC screening. In contrast to other type of cancer screening, e.g. cervical or breast, CRC screening is indeed far more complex:

- There are multiple tests (FOBT, FS and Colonoscopy), which could be used for CRC screening, and information that should be given to the patient related to each of these tests is different;

- Some CRC screening tests (e.g. Colonoscopy or FS) are invasive and have known adverse effects; and

- Some CRC screening procedures (FOBT screening test and preparation for endoscopy screening (bowel cleansing procedure)) are generally undertaken without supervision from a healthcare professional; therefore specific instructions on how to use the FOBT kit or perform the bowel cleansing procedure need to be communicated to the patient.

This complexity may generate an additional source of anxiety for patients. Communication strategies that are used in other types of cancer screening programmes may not be suitable and/or sufficient to address both CRC screening complexity and this additional source of anxiety. Moreover the success of FOBT and endoscopy screening may rely on patient's understanding of the written instructions to perform the FOBT test or the bowel cleansing procedure; how this is communicated and then acted upon is crucial. Barriers that influence comprehension of written instructions (e.g. low literacy) could be a major issue in CRC screening.

10.1.2   Purpose of this chapter

There are two primary objectives of this chapter: First, to give people involved in providing and/or managing CRC screening (e.g. managers, decision-makers, health professionals etc.) an insight into the complexity of communication in CRC screening and its related critical issues; and second, to provide them with pragmatic recommendations on information strategies/tools/interventions that could be used. These recommendations mainly refer to an organised (and centralised) CRC screening programme, as this represents the gold standard to achieve (see Chapters 1 and 2). In this communication chapter, we specifically provide guidance for FOBT screening programmes. Indeed, most of the EU countries are using FOBT as the primary screening test and more may adopt this test

based on these EU guidelines recommendations (see Chapter 4). Most of the recommendations can be applied to endoscopy programmes as well.

10.2 General principles

10.2.1 Informed decision-making, ethical principles

In the past few years, the autonomy of patients and their right to make informed decisions has become a central issue in medical interventions. Informed decision-making is a decision process in which individuals are supposed to make a rational and autonomous choice concerning their own health in order to protect themselves from risks and harms. It implies that these patients know the pros (benefits) and cons (harms) of screening and are aware not only of all the risks and benefits of participation in screening but also of non-participation (Raffle 1997; Austoker 1999; Goyder, Barratt & Irwig 2000). Receiving information about the cancer itself seems also important in the informed decision-making process (Jepson et al. 2005). As a consequence, any framework developed to communicate health information about CRC screening needs to be underpinned by the following ethical principles (Beauchamp & Childress 1979):

- Autonomy: the obligation to respect the decision-making capacities of autonomous persons. This obligation emphasises that patients should normally be in a position to choose whether to accept an intervention or not as part of their general right to determine their own lives;

- Non-malfeasance: the obligation to avoid causing harm intentionally or directly (the principle is not necessarily violated if a proper balance of benefits exists; that is, if the harm is not directly intended, but is an unfortunate side-effect of attempts to improve a person's health);

- Beneficence: the obligation to provide benefits, balancing them against risks; and

- Justice: the obligation of fairness in the distribution of benefits and risks.

Provision of balanced, unbiased and quantified information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risk factors) is crucial for helping patients in making informed decisions. It is important that scientific evidence is used to develop patient information materials, and that this evidence is easily accessible for public consultation. For example, in the UK, the summary of the evidence used in the development of the NHS National Bowel Cancer Screening Programmes patient information materials (Bowel Cancer Screening: The Facts and Bowel Cancer Screening: The Colonoscopy Investigation) is available on the NHS Cancer Screening Programme Website: http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp04.html.

10.2.2 Identifying and reducing barriers/obstacles to informed decision making

Informed decision-making (IDM) is a complex process. Receiving balanced, unbiased and quantified information related to CRC and CRC screening may be not sufficient for patients to make informed decisions; patients need also to be able to understand the information provided, to make a decision and to carry out their decision (O'Connor et al. 2009). Barriers/obstacles to IDM may exist and may be related to:

- The setting and the organisation of the CRC screening programme, such as the access and the availability of the screening service and the access and the availability of the screening information (see Chapter 2);

- The knowledge, attitudes and practice of the CRC screening provider(s) (see Chapter 2 and 10.4.2.3.3); or

- The patient themselves: age, gender (Friedemann-Sanchez, Griffin & Partin 2007), physical or mental health problems, occupation, education or abilities to read or understand information (see below) may be barriers to IDM. In some cases, risk information can be also a barrier (Steckelberg et al. 2004; Woodrow et al. 2008).

It is important to understand what these barriers are so that measures can be taken to overcome them.

10.2.2.1 Barriers related to the patients themselves

Population heterogeneity

Health professionals offering screening to the population have to deal with individuals of different ages and with different cultures, values and beliefs. For these reasons, the information provided may be viewed differently and what is best for one recipient may not be the best for another (Rimer et al. 2004; Giordano et al. 2008). In addition, contextual and personal factors may directly influence the way an individual processes health information and may therefore affect the motivations to attend screening. Educational status can also have an impact on how the presented information is understood (Aro et al. 1999; Lagerlund et al. 2000; Davis et al. 2002).

Ethnic minorities

Providers of screening programmes frequently have to cater to multicultural and multi-linguistic populations with all the related communication problems. Overcoming these problems requires more than just translating the information material. An understanding should be gained of ethno-cultural values, beliefs, health practices and communication styles of these varied groups, and the information materials produced must conform to these identified needs (van Wieringen, Harmsen & Bruijnzeels 2002).

Low health literacy

Inadequate or low health literacy is defined as the inability to read and comprehend basic health-related information. Health literacy requires a complex group of reading, listening, analytical, and decision-making skills, and the ability to apply these skills to health situations. Low health literacy is independently linked to mortality and a range of poor health outcomes (Baker et al. 2002; Dewalt et al. 2004; Sudore et al. 2006a; Sudore et al. 2006b). Poverty, ethnicity and age are also considered predictors of limited literacy (Davis et al. 2002). In most countries, low literacy is a widespread problem as is low numeracy. In the UK 16% of the population (5.2 million adults) are classified as having lower literacy (Skills for life survey 2003) and 47% (15 million adults) as having low numeracy. In a screening context, low health literacy can represent a major obstacle in understanding cancer screening information, diagnosis, treatments options, etc. This is particularly true in CRC screening as the demands of written information are perhaps greatest (see 10.1.1). In a group of US male veterans, those with low literacy were 3.5 times as likely not to have heard about colorectal cancer, 1.5 times as likely not to know about the FOBT screening test, and more likely to have negative attitudes about the FOBT (Dolan et al. 2004). Specifically, they were 2 times as likely to be worried that FOBT was "messy", and 4 times as likely to state that they would not use an FOBT kit if their physician recommended it.

In order to achieve health literacy, it is important that health and screening operators ascertain people's needs by using appropriate communication strategies, promoting access, identifying and

removing barriers/obstacles within systems, and continuously evaluating the efforts to ensure improvement.

10.2.2.2 Reducing barriers

As there are many communication interventions that could be used (Figure 10.1 and section 10.4), CRC screening programmes should identify what would be the most appropriate communication strategy(ies) to use for their target population (including specific groups); CRC screening programmes should take into account their population barriers, needs and facilitators to IDM. The information materials produced must conform to these identified information needs and facilitators. The public perspective is important for appropriate understanding of these barriers, needs and facilitators. The public should be involved when communication tools are developed.

To reduce individuals' barriers, especially related to language and ways of processing information, CRC screening should provide information in a practical and concise way, using a simple and clear language, avoiding jargon and technical terms, such as incomprehensible mathematical or statistical concepts for expressing risk, and illustrations should be used (see also 10.4.2.1). This is particularly true for written instructions on how to use the FOBT kit or perform the bowel cleansing procedure.

Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or verbal interventions.

Summary of evidence

- Developing communication strategies in CRC screening programmes is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening.

- Providing effective communication is particularly challenging in CRC screening as CRC screening is far more complex than other types of cancer screening. Communication strategies adopted/used in other types of cancer screening may not be suitable and/or sufficient to address CRC screening complexity and the additional source of anxiety generated for patients. Some screening procedures (e.g. FOBT) may rely on patient's understanding of the written instructions; how this is communicated and then acted upon is essential.

- Any framework developed to communicate CRC screening information must enable individuals to make an informed choice and should be underpinned by the four ethical principles of autonomy, non-maleficence, beneficence and justice. Informed decision making (IDM) in screening supposes that people make a rational and autonomous decision to participate, knowing the pros and cons of screening and being aware of all risks and benefits of their participation **(VI)**.

- CRC programmes should provide balanced, unbiased and quantified information about CRC (e.g. incidence, risks factors and symptoms) and CRC screening (benefits, harms and risks). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation.

- Barriers/obstacles to IDM may exist and may be related to the setting and the organisation of the CRC screening programme, the knowledge, attitudes and practice of the CRC screening provider(s) or the patient themselves.

- CRC screening programmes should identify the barriers, needs and facilitators to IDM of their target population (including specific groups) **(VI)**. An understanding should be gained of ethno-cultural values, beliefs, health practices and communication styles of the varied groups of the target population. Research should be carried out to identify how to better communicate information to low literacy groups in the population. The information materials produced (including the written instructions on how to use the FOBT kit or perform the bowel cleansing procedure) and the intervention(s) used must conform to these identified information needs and

facilitators. The public should be involved in the entire process, from identifying barriers, needs and facilitators to developing information materials.

- To reduce individuals' barriers, especially related to language and ways of processing information, the language and text format should be easy to understand and illustrations should be used. Ideally, written information should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions. This is particularly true for written instructions on how to use the FOBT kit or perform the bowel cleansing procedure **(VI)**.

Recommendations

10.1 Developing communication strategies for an organised CRC screening programme is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening **(VI - A)**.

10.2 Any framework developed to communicate CRC screening information must enable subjects to make an informed decision and should be underpinned by the four ethical principles of autonomy, non-maleficence, beneficence and justice **(VI - A)**.

10.3 CRC screening programmes should provide balanced, quantified and unbiased information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risks). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation **(VI - A)**.

10.4 CRC screening programmes should identify the barriers, needs and facilitators to informed decision making (IDM) of their target population (including specific groups) **(VI - A)**. The information materials produced, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, and the intervention(s) used must conform to these identified information needs and facilitators. The public should be involved in the entire process; from identifying barriers, needs and facilitators to developing information materials **(VI - A)**.

10.5 To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions **(VI - A)**.

10.3 Communication tools/interventions used in CRC screening programmes

Organised screening programmes generally have three distinct "communication" phases throughout the CRC screening process, where information (general or person-specific information) can be provided to participants. For a CRC FOBT screening programme, Figure 10.1 illustrates these three phases and the corresponding communication tools:

i. The invitation phase: people are invited to participate in screening. Information for this screening phase is generally provided through invitation letters and leaflets. Written instructions on how to use the FOBT kit are usually provided with the kit;

ii. The reporting results phase: people are notified of the results of their screening test. Information conveyed during this phase may be very sensitive and the communication tools must be carefully crafted to address the people's information needs;

iii. The follow-up phase: only for people with a positive FOBT result who require further assessment (colonoscopy). Usually information about colonoscopy is notified at the same time as positive results. This phase also involves information about management of the colonoscopy procedure.

Figure 10.1: Communication tools in FOBT-CRC screening
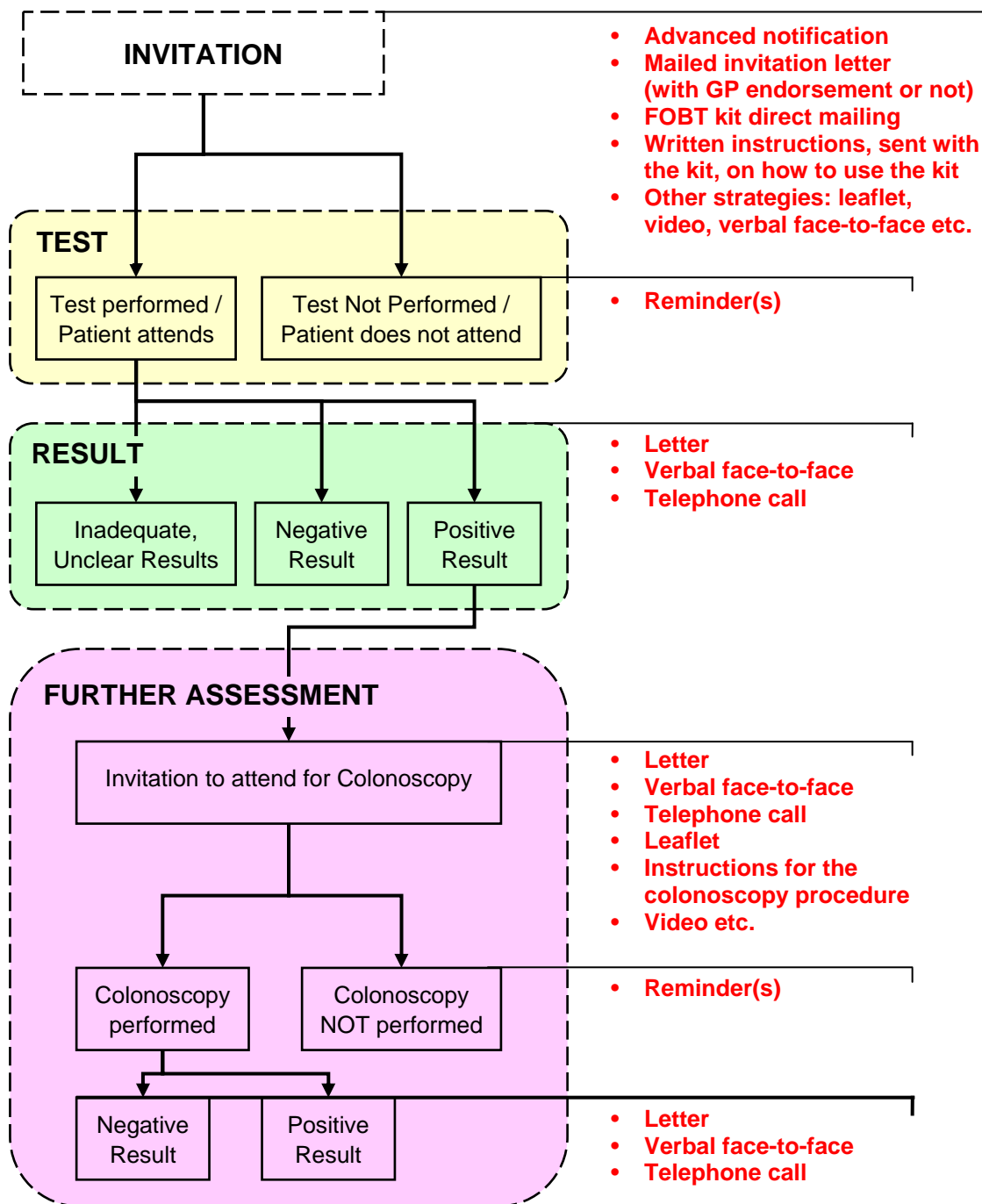
10.4 Effectiveness of communication interventions in CRC screening

In this chapter, we review all the principal communication interventions that have been used or are being used in CRC screening and assess their effectiveness and limitations. Even though it would be useful to evaluate the effectiveness of an intervention in facilitating IDM, it would be very difficult: there is a lack of agreement about the definition of IDM, and validated measures do not exist (Jepson et al. 2005; Fox 2006). As a result, the majority of studies use participation or uptake as the main outcome of interest to assess the effectiveness of a communication intervention.

10.4.1 Interventions used to invite a person undergo the test

The interventions listed in this section (10.4.1) are closely associated with the organisation of the screening programme. Therefore, they have already been discussed in detail in Chapter 2 and this discussion will not be repeated here. The Summary of evidence and Recommendations sections are the same as in Chapter 2.

10.4.1.1 Physician/GP endorsement

Summary of evidence

- The impact of information conveyed with the invitation is greater if the invitation is signed by an individual's physician. Involvement of GPs also shows a positive influence on the impact of more tailored and structured information methods **(II)**.

Recommendations

10.6 Primary health care providers should be involved in the process of conveying information to people invited for screening (see Ch. 2; Rec. 2.11; Sect. 2.4.3.4 and 2.4.3.4.1) **(II - A)**.

10.4.1.2 Letters

Summary of evidence

- A personalised letter signed by a general practitioner or by another trusted primary health care providers is more effective than an impersonal letter sent by a central screening centre **(I)**.

- An advance notification letter may increase participation **(II)**.

- Any kind of reminder is effective in increasing adherence, with telephone reminders being the most effective option, but also the most expensive **(I)**.

Recommendations

10.7 In the context of an organised programme, personal invitation letters, preferably signed by a GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation (see Ch. 2; Rec. 2.8; Sect. 2.4.3.4.1 and 2.4.3.2) **(I - A)**.

10.8 Although more effective than other modalities, phone reminders may not be cost-effective (see Ch. 2; Rec. 2.9; Sect. 2.4.3.2) **(II - B)**.

10.4.1.3 FOBT: delivery of the kit and instruction sheet

Summary of evidence

- There is no evidence that the proportion of inadequate samples may be affected by the provider used to deliver the kit, as long as clear and simple instruction sheets are provided with the kit **(II - V)**.

- The time required to reach the test provider represents a strong determinant of compliance **(II)**.

- Sending the FOBT kit together with the invitation letter may be more effective than letter alone, but the cost-effectiveness of such strategy might be low **(II)**.

Recommendations

10.9 Mailing of the FOBT kit could be a good option, but feasibility issues (such as reliability of the mailing system and test characteristics), as well as factors (such as the expected impact on participation rate) that may influence cost-effectiveness must be taken into account (see Ch. 2; Rec. 2.15; Sect 2.5.1.1) **(II - B)**.

10.10 Clear and simple instruction sheets should be provided with the kit (see Ch. 2; Rec. 2.16; Sect 2.5.1.1) **(V - A)**.

10.4.2 Other interventions which can be used with the invitation: written, visual, face-to-face interventions

10.4.2.1 Leaflets and booklets

Leaflets are a key way for the organisers of screening programmes to communicate with the target population. The results of a recently published study, in which an information leaflet was provided in addition to the invitation letter, showed that CRC participation was significantly higher among patients who read both the leaflet and the letter compared to those who read just the letter (Senore et al. 2010).

Two RCTs have investigated the effectiveness of leaflets in increasing participation in CRC screening either by FOBT (Hart et al. 1997) or colonoscopy (Denberg et al. 2006):

i.   Hart et al. (1997) showed that leaflets significantly increased participation in men but not in women. According to the authors, one possible explanation was that women are generally better informed that men about the benefits of screening as they are targeted by breast and cervical screening programmes. Hence the participation rate for women is higher than for men.

ii. Denberg et al. (2006) showed that a leaflet mailed before a scheduled appointment increased adherence to screening colonoscopy among patients receiving referrals for the procedure.

Five studies assessed the content of leaflet:

i.   One survey (van Rijn et al. 2008) was conducted to qualify the level of knowledge obtained by using a leaflet that provided information similar to that used in leaflets designed for other European screening trials. Although the leaflet was reported to be clear and readable, the information provided in it was not always well understood. The authors concluded that other educational options should be investigated in order to improve general knowledge of CRC screening in patients.

ii. In another RCT, Trevena, Irwig & Barratt (2008) assessed the relative effectiveness of using a comprehensive "decision-aid (DA) booklet" (20-page leaflet) and a 2-page leaflet that contained minimal information about false-positives and follow-up, no quantification of outcomes, no graphs or pictures, and no personal worksheet or examples. The results showed that providing more

information about FOBT screening contributed to increasing informed choice, defined by the authors as: knowledge, clear values and screening intention (decision). There was no noticeable effect on the screening uptake.

iii. Adding explanatory illustrations to written material about the polyp-cancer process and the removal of polyps during FS, significantly increased knowledge and understanding (Brotherstone et al. 2006).

iv. Robb et al.'s RCT (Robb et al. 2006) showed that using leaflets that gave information on CRC risk factors with or without information on colorectal screening by FOBT and FS was effective in increasing knowledge about the risk factors for CRC without increasing anxiety.

v. In an experimental pilot study, Lipkus et al. (Lipkus, Green & Marcus 2003) assessed the effect of adding information about CRC risks (CRC incidence and risk factors) and CRC severity (treatment modalities for CRC and two testimonials of patients living with advanced CRC) in a leaflet for FOBT screening. Whereas perception of CRC risks had no apparent effect, perception of CRC severity significantly increased intention to be screened.

Four studies have assessed the effect of using tailored/targeted leaflets/booklets:

i. Myers et al. (2007) investigated the impact of targeted and tailored interventions in an RCT by testing the effect of a leaflet addressing personal barriers to screening in one urban primary care practice. The barriers to screening were identified through a baseline telephone survey involving the entire test population. The impact of the telephone contact on the survey results is not known. The authors reported no significant difference between the interventions.

ii. Lipkus et al. (2005) assessed the effect of adding tailored information about CRC risks to a leaflet aimed at members of a specific occupational group (carpenters) by adding a section highlighting occupational risk factors that increased their personal CRC risk. The study showed that adding tailored risk factor information affected neither risk perception nor screening uptake.

iii. Marcus et al.'s RCT (Marcus et al. 2005) investigated the impact of targeted and tailored interventions on CRC screening participation outside of a primary care setting. Tailored messages were derived from a baseline telephone survey. Three tailored conditions were tested and compared to a non-tailored intervention (a booklet): a single-tailored intervention (a 16-page tailored booklet), a multiple-tailored intervention (the tailored booklet plus tailored leaflets mailed out over a 12-month period) and a multiple-re-tailored intervention (as the latter except that subsequent leaflets were "re-tailored" based on follow-up interviews). Over a 14-month period, the multiple-tailored intervention was more effective than the non-tailored one, which could be explained by the "multiple" nature of the intervention. When comparing the two multiple interventions, there was no effect of using "re-tailored" material. When age stratification was used, a significant effect of the single-tailored intervention compared to the non-tailored booklet was observed for the younger participants (ages 50-59). The impact of the baseline telephone survey is not known.

iv. Wardle et al. (2003) evaluated the effect of a leaflet specially designed for a "harder-to-reach" group of people identified in the screening arm of a FS trial. In addition to presenting basic information on CRC and screening, the booklet addressed psychological barriers to the FS test. The booklet was shown to decrease negative attitudes toward FS screening and increased screening attendance.

According to these studies, there is good evidence that leaflets can increase knowledge of CRC screening, but the evidence that leaflets facilitate the exercise of informed choice is less obvious. Fox's systematic review (Fox 2006) came to the same conclusions. As there is a lack of agreement about the definition of "informed choice" and validated measures (Jepson et al. 2005; Fox 2006), it is indeed difficult to evaluate the impact of leaflets use on patients' informed choice about CRC screening. Therefore, other interventions should be used in addition to leaflets.

Summary of evidence

- Non-tailored leaflets are effective in increasing screening participation and/or knowledge. Leaflets in addition to the invitation letter are valuable tools **(I)**.

- Including more detailed information in a leaflet (e.g. information about false-positive and follow-up, quantification of outcomes, graphs and pictures, personal worksheets or examples) contributed to an increase in knowledge, clear values and screening intention (decision) but not uptake **(I)**.

- Providing information about risk factors for CRC was effective in increasing knowledge about the risk factors for CRC without increasing anxiety. Perception of CRC risks did not affect the uptake rate for FOBT screening **(I)**.

- Adding illustrations to written material about the polyp-cancer process and the removal of the polyps during FS significantly increased knowledge and understanding **(II)**.

- Tailored leaflets for "harder-to-reach" groups seem to be effective in increasing screening participation and knowledge **(II)**.

- A tailored booklet compared to a non-tailored proved more effective in increasing participation of younger participants. A multiple-tailored intervention over a period of time was more effective than using a non-tailored booklet **(II)**. However, the impact of the baseline telephone survey to tailor the materials in this study cannot be evaluated.

- When using multiple-tailored interventions, there was no effect of using "re-tailored" material **(II)**.

- It is difficult to prove that leaflets facilitate the exercise of IDM **(I)**.

Recommendations

10.11 Use of a non-tailored leaflet for the general population is advised; the leaflet should be included with the invitation letter. Information about CRC screening risks and benefits, CRC risks (incidence and risk factors), meaning of test results, potential diagnostic tests and potential treatment options should be included **(VI - A)**. Illustrations may be used, which would be particularly useful for minorities, elderly or low-literacy participants **(II - A)**.

10.12 A tailored leaflet for "harder-to-reach" groups could be used if these groups can be identified. **(II - B)**.

10.13 Although there is good evidence that leaflets can increase knowledge of CRC screening, there is inconclusive evidence on the impact of leaflets on informed decision making (IDM). As a consequence, other interventions should be used in addition to leaflets **(VI - A)**.

10.4.2.2 Videotapes/DVDs, interactive computer-based decision aids, ICTs (information & communication technologies) and Internet

10.4.2.2.1 Videotapes/DVDs

a. Non multi-modal intervention

Two US studies (Friedman et al. 2001; Zapka et al. 2004) showed that using a videotape had no effect on the overall rate of CRC screening. In the second study the video, mailed before a scheduled examination, only modestly improved sigmoidoscopy screening rates.

Two studies by Griffith et al. (2008) investigated the effect of introducing differential content in a DVD. In the first study, the DVD presented to both groups differed only in the inclusion of a segment where an individual discussed why he did not participate in screening. In the second study, two forms of a DVD were evaluated: one included two screening test options, and the other five screening test options. Participants' interest in CRC screening was investigated; neither study found a difference between the interventions.

Meade, McKinney & Barnas (1994) investigated whether a booklet or a videotape, both tailored to the target population of participants, was more effective for improving CRC knowledge, which was evaluated just after the intervention. Results indicated that both booklet and videotape significantly increased knowledge and there were no statistically significant differences between the 2 interventions, regardless of the patients' literacy levels. The "tailored" aspect of both of the interventions was one hypothesis to explain the absence of discrepancy between the two interventions.

b. Multi-modal intervention including videotape/DVD and print material

Four studies (Pignone, Harris & Kinsinger 2000; Campbell et al. 2004; Powe, Ntekop & Barron 2004; Lewis et al. 2008) assessed the effect of using a multi-modal intervention, which included a videotape and print material:

i. Pignone et al.'s (Pignone, Harris & Kinsinger 2000) RCT trial used an educational videotape, targeted brochure and chart marker. The study showed that the intervention, compared to no intervention, increased CRC screening participation.

ii. In Lewis et al.'s (Lewis et al. 2008) controlled trial the intervention consisted of a mailed package containing an educational videotape, a reminder letter from their physician, surveys to be completed before and after the video watching, and system changes allowing patients direct access to schedule screening tests. The study showed that the intervention, compared to no intervention, increased CRC screening participation.

iii. Campbell et al.'s (Campbell et al. 2004) randomised trial compared the effect of a tailored print and video intervention (4 personalised computer-tailored newsletters and videotapes), designed to target a rural minority (African-American) community, to a lay health advisor (a trained member of the community) intervention. The study showed that the tailored print and video intervention was more effective in increasing FOBT screening than no intervention. The authors reported suboptimal advisor reach and diffusion.

iv. Powe, Ntekop & Barron (2004) showed that a 5-phase culturally relevant intervention (video, calendar, poster, brochure, flier) among community elders and delivered over a 12-month period, significantly increased knowledge and screening participation compared to either a 6-month and 3-phase intervention or a single intervention (video or usual care). However, it is not possible to determine which aspects of the multi-modal intervention were most effective.

Summary of evidence

- A DVD alone had no effect on screening rates or interest in screening. Changing the video content did not affect this result. No difference was found between a tailored booklet and a tailored DVD regardless of the patients' literacy levels **(I)**.

- When a video/DVD was used in a multi-modal intervention, an improvement in knowledge and increase in screening rates was observed. When the components of the multi-modal interventions were provided successively over a period of time, increasing the number of components and the period over which they were provided, there was an increased in knowledge and in participation of elderly people **(I)**.

Recommendations

10.14 Video/DVD may be a useful component in a multi-modal intervention in addition to written information and would be particularly useful for the elderly, minorities and low literacy participants **(I - B)**. For the elderly, increasing the number of components of the multi-modal intervention and the period over which these components are provided may be more effective **(I - B)**.

10.4.2.2.2 Interactive computer-based decision aids

Four studies (Dolan & Frisina 2002; Kim et al. 2005; Miller Jr. et al. 2005; Menon et al. 2008) showed that a computer-based decision aid improved patients' knowledge about screening and was useful to most in making decisions about screening (increased intention to be screened and increased interest in screening). The same results were obtained in rural primary care practices (Geller et al. 2008) and in a Hispano/Latino community (Makoul et al. 2009) for which the decision aid was specifically designed.

Three studies have assessed the effect of a computer-based decision aid on screening participation:

i.   An RCT by Ruffin et al. (Ruffin, Fetters & Jimbo 2007) showed that an interactive programme to help to establish a preference among the CRC screening tests options was more effective than an existing CRC website selected to represent the standard, state-of-the art and non interactive website.

ii. In an uncontrolled trial, Kim et al. (2005) tested the effect of an interactive computer-based decision aid including an audio track playing during the entire programme and explaining all of the figures that were presented, making the content accessible to users with varying levels of literacy. The intervention improved screening uptake.

iii. Dolan and Frisina's (Dolan & Frisina 2002) RCT showed that a computer-based decision aid designed to help patients choose between different strategies for CRC screening and including the option of 'no screening', when added to a simple educational interview intervention, had no effect on CRC screening uptake.

Jerant et al. (2007) conducted an RCT comparing the effects of using a tailored versus a non-tailored interactive multimedia program. Besides a tailored component (e.g. specific screening recommendation tailored to the individual), the tailored programme also contained brief patients and physician video clips that were not in the non-tailored intervention. The study showed that the tailored programme was significantly more effective in bolstering CRC screening readiness and self-efficacy than the non-tailored intervention. It is not clear to what extent the video clips component of the tailored computer-based decision aid contributed to the result.

Summary of evidence

- Interactive computer-based decision aids improved knowledge and were useful in helping people decide whether or not to be screened. The same results were obtained in rural primary care practices and in an ethnic community for which the decision aid was specifically designed **(I)**.

- Interactive computer-based decision aids increased screening participation, but had no effect if added to an interview intervention. A tailored computer-based intervention affected knowledge and intention to be screened more than a non-tailored intervention, but it is not clear to what extent the video clips component of the tailored computer-based decision aid contributed to the result **(II)**.

Recommendations

10.15 A computer-based decision aid could be used to help both the general population and specific groups to make informed decisions about CRC screening **(I - B)**. The computer-based decision aid should be "user-friendly" and designed to fit with the computer abilities of the target population (general or specific groups).

10.4.2.2.3 Information and communication technologies: future promises and challenges for enhancing CRC screening delivery

Information and communication technologies (ICTs) are a diverse set of technological tools and resources used to communicate, create, disseminate, store, and manage information. ICT is sometimes referred to as simply Information Technologies (IT). ICTs include computers, the Internet,

broadcasting technologies (radio and television), and telephones. They are typically used in combination rather than singly.

The European Union's Commission for Information Society and Media has defined eHealth as ICT-based tools covering "the interaction between patients and health-service providers, institution-to-institution transmission of data, or peer-to-peer communication between patients and/or health professionals" (http://ec.europa.eu/information_society/activities/health/whatis_ehealth/index_en.htm). Examples include health information networks, electronic health records, telemedicine services, wearable and portable systems which communicate, health portals, and many other ICT-based tools assisting disease prevention, diagnosis, treatment, health monitoring and lifestyle management.

According to a recent systematic review (Jimbo et al. 2006), the published research using ICT in the context of cancer screening in general and CRC screening in particular almost exclusively tested the impact of ICT-generated reminders to either the provider alone or to both the patient and the provider. Dexheimer et al.'s review (Dexheimer et al. 2008), found that ICT tools used to generate reminders, were either "computer-generated" (ICT tools were used to identify eligible patients and were integrated with electronic appointment systems so that reminders were automatically printed in advance of patient appointments and placed in the patient's chart) or "computerized" (ICT were used to identify eligible patient and generate electronic prompt).

There is ample evidence that patient- and provider-directed computerised reminder systems increase adherence in other cancer screening fields e.g. mammography. For CRC screening, three out of four recent studies showed that ICT-generated reminders to physicians increased CRC screening:

i.   Sequist et al. (2009) used computerized reminders, in both a passive and active form, added within each patient's electronic medical record, and thus visible by their physician during the appointment. Results showed that electronic reminders tended to increase screening rates among patients with 3 or more primary care visits.

ii.   Chan & Vernon (2008) tested the feasibility of using the NetLET website interface to provide patients with a personalised reminder from their physician to undergo CRC screening. The study concluded that it was not feasible to implement the NetLET. For the authors the lack of success was essentially due to the e-mail access barrier (patients without email at home or work) and the ICT system barrier itself, i.e. the complexity of accessing the NetLET website.

iii. Nease et al. (2008) investigated the effect of a computer-generated reminder placed in the patient's chart. The study showed that 11 out of 12 practices significantly increased their CRC screening rates and there was no significant difference between sending reminders either to clinician alone or to both patient and clinician.

iv.   Jimbo et al.'s review (Jimbo et al. 2006) identified 13 studies evaluating the effect on ICT-generated reminders in FOBT CRC screening: 8 out of 13 studies showed that reminders increased FOBT screening participation.

According to the EU commission (Information Society and Media), the widespread implementation of ICT in health will increase the quality of healthcare services and will provide:

- Better information for patients and healthcare professionals;

- More efficient organisation of resources; and

- More "patient-friendly" healthcare services by helping healthcare providers to be more flexible and better able to address the differing needs of individual patients.

Still "poverty and illiteracy in developing nations are major barriers to the adoption and sustainability of information technologies" (Abbott & Coenen 2008). Nevertheless, the existence of many successful implementations of ICT-enabled health communications and electronic health record systems in less industrialised countries in Africa (Abbott & Coenen 2008), suggests that it is possible to bypass these barriers.

For Vernon & Meissner (2008), ICT is one of the "Six elements of a New Model of Primary healthcare delivery" in colorectal cancer screening. ICT use for interventions in screening in general, and in CRC screening more specifically, has the potential to go beyond simple reminder systems (Jimbo et al. 2006; Vernon & Meissner 2008). But to widely realise the potential of the use of IT in screening, patients' charts must provide the infrastructure to do this. Patients' charts must be organized enough to determine patient screening status and ideally physicians and clinics should use electronic medical records. According to Vernon & Meissner (2008) and Dexheimer et al. (2008), these are areas that clearly need to be improved.

Summary of evidence

- ICT-generated reminders to physicians increased CRC screening rates **(I)**. ICT has an important role to play in increasing efficiency of CRC screening and has the potential to go beyond simple reminder systems, and will provide better information for patients and healthcare professionals, more efficient organisation of resources and more "patient-friendly" healthcare services by providing a more flexible and personalised approach **(I)**.

- To widely realise the potential of the use of IT in screening, patients' medical records should be improved to easily determine patient screening status, and ideally should be electronic **(I)**.

Recommendations

10.16 ICT-generated reminders to physicians could be used as an opportunity to provide counselling to patients on CRC and CRC screening, if primary care or other health practitioners are involved, and if patient medical records are electronic and give screening status **(I - A)**.

10.4.2.2.4 Internet

There is no evidence of the impact of the internet on screening in general and more specifically on CRC screening. Based on Della et al's review (Della et al. 2008), the popularity of the internet as a conduit for health information is increasing. Still, not everyone is online; research indicates that higher usage of the internet is associated with younger age, more education and higher income (Fox & Rainie 2000; Pereira et al. 2000; Brodie et al. 2001; Della et al. 2008). As the variety of health information on the internet is expanding, source credibility continues to be a pivotal factor in determining the quality of information (Della et al. 2008). James et al. (2007) performed a study of information seeking by cancer patients and their caregivers. This study has shown that "those who accessed Internet information, either directly or indirectly, reported high levels of satisfaction with it and generally rated it more highly than booklets or leaflets". The authors concluded that "the internet is an effective means of information provision in those who use it. Facilitated internet access and directed use by health professionals would be effective way of broadening access to this medium."

Summary of evidence

- There is no evidence of the impact of the Internet on CRC screening **(VI)**.

- The popularity of the Internet as a conduit for health information is increasing **(VI)**.

- People with younger age, more education and higher income have higher usage of the Internet **(V)**.

- Source credibility continues to be a pivotal factor in determining the quality of information **(V)**.

- Generally, using the internet as a source of information about cancer is more satisfying than leaflets or booklets **(VI)**.

Recommendations

10.17 If possible, all information provided by the screening programme should be available on a specific web site. This information should be regularly updated **(VI - A)**.

10.4.2.3 Telephone intervention, patient navigator (PN) intervention, and verbal face-to-face intervention other than PN

10.4.2.3.1 Telephone intervention

The majority of the studies assessed the impact of a reminder tailored telephone call added to printed materials (the "usual care"), which were incrementally added. In some studies, the intervention also included a booklet/leaflet/brochure sent before the call.

We retrieved seven studies:

i.   Turner et al.'s RCT (Turner et al. 2008) compared a phone call by a trained peer coach with a mailed colonoscopy brochure about CRC screening in improving adherence to a first scheduled colonoscopy. Seven trained older patients who had had a colonoscopy served as peer coaches. The calls (1 per patient) were scheduled within two weeks of the colonoscopy appointment to address barriers to attendance. In this study peer coach telephone support significantly increased colonoscopy attendance. The fact that coaches received payment for each completed patient call might have introduced a bias in the study.

ii. In Braun et al.'s RCT (Braun et al. 2005), the number of telephone calls has been suggested to have a negative effect on screening. The authors compared an intervention (one culturally targeted educational presentation) delivered by a nurse to an intervention delivered by physician and a peer, both of the same community background as the participants. The first intervention also included one reminder call, whereas the second intervention included multiple reminder telephone calls to encourage screening and address barriers. The two interventions realized similar gains in CRC knowledge but the education provided by the nurse was more effective in increasing uptake of CRC screening; one hypothesis to explain this result was that the multiple reminder phone calls made the intervention too invasive and burdensome.

iii. Lairson's RCT (Lairson et al. 2008) compared a usual care intervention (invitation letter, FOBT test, booklet and reminder letter) to tailored interventions, which incrementally added a tailored leaflet (two message pages) and a reminder telephone call to the usual care intervention. The most effective intervention was the intervention that used the tailored leaflet and the tailored telephone call reminder. An economic analysis showed that it was also the most costly.

iv. Three RCTs were performed either in a primary care population (Costanza et al. 2007), at worksites for automobile industry employees (Tilley et al. 1999), or in an HMO association (Myers et al. 1994). These studies compared standard intervention to an intervention including printed materials along with tailored telephone outreach. In Costanza's RCT, the intervention did not increase colorectal cancer screening compared to control. In Tilley's RCT, the authors concluded that the tailored intervention (mailed invitation, tailored booklet followed by a tailored telephone call) produced a modest but higher screening participation compared to standard intervention (personal letters and flyers at the worksites). In Myers et al.'s survey (1994), adding to the control intervention (a FOBT kit and a reminder letter) a brochure followed by a phone call increased participation comparing to the control intervention.

v.   Myers et al. (1991) tested the effect of using usual care (i.e. mailing an advance letter, FOBT kit and a reminder letter) followed either by one telephone call intervention or by two calls plus a brochure intervention. The telephone outreach was used to resolve patient's barriers to non adherence or answer patient-specific questions. The study showed that one call significantly increased the participation compared to usual care. Moreover two calls seemed to have more impact than one on the participation rate.

Even if a tailored telephone call intervention seemed to be effective, it could certainly not be applicable as part of the normal invitation process in CRC screening for reasons of cost-effectiveness and the high volume of calls to be processed. It may be possible to implement tailored telephone calls for harder-to-reach groups if these groups can be identified.

Summary of evidence

- The majority of the studies assessed the impact of tailored reminder telephone call on CRC screening participation.

- A tailored telephone intervention seemed to be effective in increasing screening participation when used as a reminder to mailed invitation materials (usually booklet, FOBT kit, and mailed letter). The most effective but also the most costly intervention was to add to usual care a tailored leaflet and a tailored telephone call reminder.

Tailored telephone calls could certainly not be applicable as part of the normal invitation process for CRC screening for reasons of cost-effectiveness and the high volume of calls to be processed. It may be possible to implement tailored telephone call for "harder-to-reach" groups if these groups can be identified **(II - B)**. For example, peer coach telephone support for explaining colonoscopy procedure seemed to improve attendance for colonoscopy **(II)**. It has been suggested that multiple reminder phone calls could make the intervention too invasive and burdensome.

Recommendations

10.18 It is not cost-effective or feasible to implement a tailored reminder telephone call in the general population. It may be possible for CRC screening programmes to use such an intervention for harder-to-reach groups if these groups can be identified **(II - B)**. For example peer telephone support could be used especially to decrease the attendance barrier to colonoscopy **(II - B)**. Multiple telephone calls seem to have more effect, but it is important to avoid coercion **(I - C)**.

10.4.2.3.2 Patient navigation/patient navigator

A patient navigator (PN) is an individual whose role has been described as providing individualized assistance (by telephone and/or by direct contact) to a patient to both educate and help them overcome healthcare system barriers related to, for example, doctors' offices, clinics, hospitals, out-patient centres, payment systems. In cancer screening, patient navigation should be considered as a method for guiding individuals through the cancer screening process (Myers et al. 2008). "The client navigator approach included the traditional method (i.e. educated patients about cancer screening) along with a social worker who 'navigated' the health care system" (Jandorf et al. 2005). By being able to provide social and logistical services, PN intervention should be differentiated from the usual "telephone intervention" (above section) or "verbal face-to-face intervention" (next section). Social and logistical services provided by patient navigators could be for example facilitating communication among patients/family members/survivors/healthcare providers, coordinating care among providers, facilitating appointments and follow-up appointments, and facilitating access and transportation to services facilities. Patient navigators could be trained community health workers/advisors who have close ties to the local community or trained social workers/health professional/volunteers or belong to a specific organization. The American Cancer Society (ACS) Patient Navigator Program, launched in 2005, currently operates in 60 sites across the USA. The ACS navigators are concentrated in hospitals and clinics that treat a large number of medically underserved patients.

Summary of evidence

- We retrieved eight recent US studies that examined the impact of involving PN in CRC screening in either urban public hospitals setting (Myers et al. 2008) or minority/ethnic urban community health centres (Jandorf et al. 2005; Basch et al. 2006; Dietrich et al. 2006; Nash et al. 2006; Christie et al. 2008; Lasser et al. 2008; Percac-Lima et al. 2009). In the minority/ethnic community, the PN was from a similar ethnic background and/or lived in the community from which the participants were recruited. Patient navigator intervention significantly increased the screening participation. The results of Myers et al.'s pilot study (Myers et al. 2008) are currently being tested in two RCTs.

Recommendations

10.19 Patient navigation could be used within CRC screening programmes, particularly to reach subgroups of the population such as the elderly, those with low literacy, and medically underserved patients. When used with minorities, the PN should be from a similar ethnic background and/or live in the same community as the participant **(I - B)**.

10.4.2.3.3 Verbal face-to-face intervention other than PN: verbal face-to-face with GP, nurse or other health or trained non-health professional

As assessed by Wee et al.'s study (Wee, McCarthy & Phillips 2005), and other studies detailed in Chapter 2, primary care physician (GP) counselling of patients has been positively associated with increasing CRC screening participation rates.

We retrieved eight studies that assessed the impact of direct interaction other than GP (e.g. face-to-face with nurse or other health or trained non-health professional) with participants either in the general population or in some specific subgroups of the general population, such as the socio-economically disadvantaged and/or belonging to racial/ethnic minority groups.

a. In the general population

Two studies (Thompson et al. 2000; Stokamer et al. 2005) evaluated the effect of one-to-one/face-to-face education about the FOBT screening process (purpose/technique of obtaining samples/further testing) provided by a nurse and showed that the intervention increased the return rate of FOBT kits. Stokamer et al. (2005) also reported that participants in the intervention group were significantly less likely to contact the clinic with additional questions. In Thompson et al. study, the nurse was also allowed to order FOBT kits that were given to patients before they left the clinic. This study showed an increased number of ordered kits.

Courtier et al. (2002), evaluated the impact of a trained, non-healthcare professional who provided in-home information and a FOBT kit and personally collected the specimens from the participant's home. The study showed that CRC screening participation was higher in the intervention group.

In Hudson's study (Hudson et al. 2007), practices that reported using nursing or health educator staff to provide behavioural counselling to patients on topics such as diet, exercise or tobacco also resulted in significantly increased CRC screening rates.

b. In some specific sub groups of the general population

Ford et al.'s RCT (Ford, Havstad & Davis 2004) tested different combinations of mail, reminder mail and call, phone call and in person church-based recruitment to invite older (55–74 years) African-American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. They concluded that the most intensive intervention increased significantly the participation compared with the control or the other interventions. The most intensive intervention was the one that besides mail, telephone call, and reminder telephone call, added a face-to-face contact with participants (one session held at church).

Katz et al. (2007) showed in a non-randomised trial that a community-based intervention (a face-to-face interview delivered by trained volunteers from the communities) performed among low-income women (78% African-American) led to a significant increase in positive beliefs about CRC screening and in the intention to complete CRC screening in the next 12 months after the intervention. However CRC screening rates were not significantly increased 1 year after the intervention.

Based on Gren et al.'s paper (Gren et al. 2009), the American PLCO (The Prostate, Lung, Colorectal and Ovarian Cancer) screening trial of centres with enhanced minority recruitment programmes, relied

extensively on community outreach, particularly church-based recruitment and in-person information sessions, to meet their goals.

c. Quality of counselling

In an observational study Ling et al. (2008) evaluated a provider's (physician and nurse practitioner) intervention about CRC screening. They coded each intervention for nine elements of communication (Informed Decision-Making (IDM) Model) that have been shown to be important for IDM. The study showed that 6 of the 9 elements occurred in ≤20% of the visits with none addressed in ≥50%. In this study, compared to patients whose understanding was not assessed, patients whose understanding was assessed during the visit had a higher rate of completing CRC screening. On the contrary, CRC screening participation was less when "patient's screening test preference" or "pros and cons of the alternatives" was discussed.

Ferreira et al.'s RCT (Ferreira et al. 2005) assessed the effect of trying to improve healthcare providers' (nurse practitioner and residents) counselling by using an intervention directed to the health-care provider. The intervention was a series of workshops on rationale and guidelines for CRC screening, and on strategies for improving communication with patients with low literacy skills. During the study, the healthcare providers received confidential information on their individual recommendation and adherence rates. The intervention significantly increased both recommendations and CRC screening completion (FOBT, endoscopy) among patients. The intervention also increased the screening rates among patients with low literacy skills.

Summary of evidence

- Verbal face-to-face intervention and education (nurse and GP) were clearly useful in improving knowledge and participation in CRC screening **(I)**.

- A trained non-health professional, who provided in-home information and a FOBT kit and personally collected the specimens from the participant's home, was effective in increasing CRC screening **(II)**.

- Practices, that reported using nursing or health educator staff to provide behavioural counselling to patients on topics such as diet, exercise or tobacco, also resulted in significantly increased CRC screening rates **(V)**.

- All the elements that should be discussed by GP/nurse to help patients in making informed decisions seemed not to be used **(V)**. Some of these elements seemed to influence patient participation in CRC screening.

- Nurse practitioner/resident training (about CRC screening and communication strategies) and performance communication significantly increased both CRC screening recommendations and completion among patients in general and patients with low literacy skills **(VI)**.

- Community-based interventions such as church-based sessions or in-person interviews significantly increased CRC participation or the intention to be screened in minority subgroups of the US population, especially in the elderly **(II)**.

Recommendations

10.20 Verbal face-to-face interventions with a nurse or physician could be used to improve knowledge and participation. They would be useful to reach subgroups of the population such as the elderly, minorities and those with low literacy **(I - A)**.

10.21 Nurses and primary care practitioners (GPs) should receive adequate training to be able to help patients in making informed decisions about CRC screening **(VI - A)**.

10.22 Community-based verbal face-to-face interventions such as church-based sessions or in-person interviews could be used to reach minorities, in the case where the providers of such interventions received adequate training **(II - B)**.

10.4.2.4 Mass media campaigns

A Cochrane systematic review (Grilli, Ramsay & Minozzi 2002) supports the view that mass media campaigns may have a positive influence upon the way health services are utilised, while the effect on promoting cancer screening is less clear.

Two studies conducted in the late 1980s combined the free distribution of FOBT kits through pharmacies with repeated educational reports on a local television station (McGarrity et al. 1989; McGarrity, Long & Peiffer 1990). However, neither study included any outcomes addressing the effect advertisements may have had on participation rates or decision-making. A cross-sectional survey (Schroy III, et al. 2008) aimed at assessing the extent to which mass media campaigns launched since the year 2000 in the USA have achieved the goal of educating the public about CRC and screening. Although the authors concluded that media campaigns can be effective in increasing public awareness about CRC risk, the study was not designed to support this assertion.

Two studies were identified that reported the effect on CRC screening rates after extensive media coverage involving celebrities:

i.   In the first study, Brown & Potosky (1990) reported various outcomes related to media coverage of US President Ronald Reagan's CRC episode in July 1985. The authors reported that there was a transitory increase in public interest in CRC, with a corresponding increase in early detection tests following media coverage of the President's CRC surgery. However, as stated by the authors, the evidence is only suggestive and the methodology of the study quite poor.

ii.   The second study assessed the impact of a CRC awareness campaign on colonoscopy investigations by a well-known television celebrity (Cram et al. 2003). The study found that the awareness campaign was temporally associated with an increase in colonoscopy rates. The authors concluded that a celebrity spokesperson can have a substantial impact on public participation in screening programmes.

Nicholson et al.'s RCT (Nicholson et al. 2008) has shown that the way information about colorectal cancer was reported in a medium could influence the motivation to be screened in minority groups: information emphasising the progress African-Americans were making in increasing CRC screening and decreasing CRC mortality led to significantly increase intention to be screened, and counteracted the negative effects of medical mistrust, compared to information emphasising racial disparities.

As media can be a source of information for patients, those in charge of CRC screening programmes should work closely with the media and provide them with up-to-date, accurate and comprehensive information to prevent contradictory, false messages or false expectations being sent to the public.

Summary of evidence

Several studies have investigated the role that the mass media may have in increasing participation in CRC screening. Unfortunately, the quality of the published studies is quite poor, with the majority failing to include any outcomes assessing the role or effect that advertisements or mass media may have either on the decision-making process or the decision to participate or not in CRC screening.

- Celebrity campaigns were useful to increase participation but the increase was only temporary **(V)**.

- Information emphasising the progress a minority group was making in increasing CRC screening and decreasing CRC mortality led to significantly increase intention to be screened, and counteracted the negative effects of medical mistrust, compared to information emphasising racial disparities **(II)**.

As the media can be a source of information for patients, those in charge of CRC screening programmes should work closely with the media and provide them with up-to-date, accurate and comprehensive information.

Recommendations

10.23 Mass media campaigns using celebrities may be used to increase the awareness of CRC and CRC screening programmes. However, they should be complemented by other measures as the effects are only temporary **(V - C)**.

10.24 When addressed to minority groups, information provided by mass media campaigns should emphasise positive progress made by the minority group instead of emphasising racial disparities **(VI - C)**.

10.25 (See below).

10.4.2.5 Advocacy groups

Advocacy groups are playing an increasing role in promoting cancer screening (Ganz 1995). In colorectal cancer screening, for example, we can refer to the role played by the European Cancer Patient Coalition in the generation of CRC awareness and lobbying for effective CRC screening programmes in Europe. However, there are at present no studies showing the impact of such groups on CRC screening. The role of advocacy groups should be investigated. However, as advocacy groups can be a source of information for patients, e.g. by disseminating education messages to the target audience and providing supportive care during and after treatment patient, screening organisations should share information with advocacy groups to prevent contradictory messages being sent to the public.

Recommendations

10.25 CRC screening programmes should work closely with advocacy groups and the media and provide them with up-to-date, accurate and comprehensive information about CRC and CRC screening **(VI - A)**.

10.4.3 Communication tools/interventions used to inform a person of a screening test result and facilitate follow-up of a positive result

In CRC screening, positive results are usually accompanied by information about follow-up. Miglioretti et al. (2008) reported that 16% of patients refused follow-up after a positive FOBT test. A similar figure is reported in many countries worldwide. This result emphasises the need for vigilance and continued effort at patient-centred communication and counselling (Zapka 2008).

Very little is known regarding which interventions should be used to ensure follow-up of patients with abnormal findings in CRC screening. Based on a 2004 systematic review (Bastani et al. 2004), it seems that various interventions such as mail and telephone reminders, telephone counselling, and print educational interventions are effective in increasing follow-up rates of abnormal cancer screening findings. In this review, just four studies were retrieved related to CRC screening. Among these studies, Myers et al.'s RCT (2004) has shown that a reminder-feedback and an educational outreach intervention targeted to the primary care physician were effective in improving follow-up.

A retrospective chart review study (Rao, Schilling & Sequist 2009) has shown that one factor associated with higher rates of colonoscopy after positive FOBT results was the patient having a consultation with a gastroenterologist.

Rubin et al.'s RCT (Rubin et al. 2007) has shown that providing patients with a written copy of their standard colonoscopy screening report at the conclusion of their procedure enhanced recall of the findings and recommendations.

Zheng et al. (2006) investigated the factors relating to adherence to follow-up after an abnormal screening FOBT result. The results of this survey suggest that future interventions should focus on:

- Clarifying misperceptions about follow-up (e.g. understanding the benefits and meanings of follow-up);

- Promoting the acceptance of colonoscopy, as for example patients could perceive unpleasantness regarding preparation for colonoscopy and discomfort of the procedure. Turner et al.'s (Turner et al. 2008) result supports this finding: a peer coach telephone support, in which former patients who had had a colonoscopy served as peer coaches, scheduled within 2 weeks of the colonoscopy appointment significantly increased screening colonoscopy attendance; and

- Addressing psychological distress (e.g. being afraid of finding cancer), and making follow-up testing more convenient and accessible.

Regarding patient consent, verbal face-to-face intervention before (pre-assessment) and after the endoscopic procedure for programmes undergoing endoscopy (FS or colonoscopy) either for primary screening, or more specifically, as recommended by the EU, for assessment of abnormalities detected in FOBT screening (follow-up): see summary below and Chapter 5 for more details.

Summary of evidence

- A reminder-feedback and an educational outreach intervention targeted to the primary care physician can be effective in improving follow-up. Providing patients with a written copy of their standard screening report enhanced recall of the findings and recommendations **(II)**.

- Using peer coach telephone support increases colonoscopy attendance: interventions should focus on clarifying misperceptions about follow-up, promoting the acceptance of the follow-up procedure, addressing psychological distress and making follow-up testing more convenient and accessible **(II)**.

- Obtaining a consultation with a gastroenterologist increases the rates of follow-up colonoscopy **(V)**.

The patient should give consent to the endoscopy procedure and should have the opportunity to withdraw consent at any stage before or during the procedure. Patients should be informed about the outcome of their procedure both orally and with written information before leaving the endoscopy unit. The outcome of screening examinations should be communicated to the primary care doctor or equivalent (see Chapter 5 for more details).

Recommendations

10.26 A telephone or ideally a verbal face-to-face intervention, e.g. nurse or physician intervention, should be used to inform a patient of a positive screening test result, as obtaining such a result could be a source of psychological distress for the patient. A letter informing the patient should not be used as the only way of notifying a positive result **(VI - A)**.

10.27 To increase endoscopy follow-up after a positive FOBT and facilitate communication, CRC screening programmes should, where possible:

  o Use a reminder-feedback and an educational outreach intervention targeted to the primary care physician **(II - A)**;

  o Provide patients with a written copy of their screening report **(II - A)**;

  o Facilitate patient consultation with a gastroenterologist **(V - B)**;

  o Describe the follow-up procedure, make the follow-up testing more convenient and accessible **(VI - A)**; and

    o Use direct contact intervention to address psychological distress and other specific barriers **(V - B)**.

From Chapter 5 (see Chapter 5 for more details):

10.28 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see Ch. 5, Rec. 5.20, Sect 5.3.2) **(III - B)**.

10.29 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see Ch. 5, Rec. 5.25, Sect 5.3.1) **(VI - B)**.

10.30 Patients should be informed about the outcome of their procedure before leaving the endoscopy unit and given written information that supports a verbal explanation (see Ch. 5, Rec. 5.26, Sect 5.4.3) **(VI - A)**.

10.31 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see Ch. 5, Rec. 5.27, Sect 5.5.5) **(VI - B)**.

10.5 Content that should be included in: the invitation letter and leaflet, the letter and leaflet used to notify results, and the instructions

10.5.1 General recommendations

Summary of evidence

In organised CRC screening programmes, letters and leaflets are the two most disseminated communication instruments used by health organisations. Letters are generally used to invite people to participate in CRC screening, to notify them of the result of the test and provide information on follow-up. Written materials have advantages such as flexibility of delivery, portability, reusability and can be produced relatively quickly and inexpensively. But they have some obvious limitations: information must be concise, addressed to a general readership and is not effective for individuals who do not read. Leaflets should be used to support and detail the information provided in the letters. Some basic information must be included in the letter in case a person reads only the invitation letter and not the leaflet. Screening programmes should ensure that participants understand the instructions on how to use the FOBT kit and perform the bowel cleansing. Letters, leaflets and written instructions should be developed taking into account all the recommendations given previously.

Currently there is no consensus on what should be said in the letter/leaflet even if the majority of experts agree that individuals must be given information about the pros and the cons of screening to enable IDM. The material listed below could be used as guidelines/examples:

- The recent EU guidelines for cervix cancer screening;

- The IPDAS (an international group of more than 100 researchers, practitioners and stakeholders, see following chapter) recommendations for information content (Elwyn et al. 2006);

- The ICSN publication, 2007: "Designing Print Materials: A Communications Guide for Breast Cancer Screening", (National Cancer Institute (NCI) 2007);

- The invitation leaflet developed and used for the UK CRC screening programme (The NHS Bowel Cancer Screening Programme: "Bowel Cancer Screening: the Facts", http://www.cancerscreening.nhs.uk/bowel/publications/bowel-cancer-the-facts.pdf, and the Evidence Summary: patient information for the NHS Bowel cancer screening programme);

- The colonoscopy leaflet developed and used for the UK CRC screening programme (The NHS Bowel Cancer Screening Programme, "Bowel Cancer Screening: The colonoscopy; investigation", http://www.cancerscreening.nhs.uk/bowel/publications/colonoscopy-investigation.pdf); and/or

- The invitation and colonoscopy leaflets developed and used for the UK CRC screening programme for those with disabilities: http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp-learning-disabilities-leaflet.pdf and http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp-colonoscopy-learning-disabilities-leaflet.pdf

Recommendations

Letters, leaflets and written instructions (on how to use the FOBT kit and perform the bowel cleansing) should be developed by taking into account all the recommendations below, some of which are either taken from previous relevant sections of Chapter 10 as indicated:

- General principles (Paragraph 10.2): recommendations 10.1–10.5.

- Physician/GP endorsement, Letters, FOBT delivery and instructions (Paragraph 10.4.1): recommendations 10.6, 10.7, 10.10.

- Leaflets/booklets (Paragraph 10.4.2.1): recommendations 10.11–10.13.

- Result and follow-up (Paragraph 10.4.3 and Chapter 5): 10.27–10.31.

New recommendations

10.32 Ideally, the invitation letter and the letter used for notification of a positive result should be sent with a leaflet and participants should be encouraged to read it **(VI - A)**.

10.33 Certain basic information e.g. logistic/organisational information, a description of the screening test, the harms and benefits of screening, information about the FOBT kit and the bowel cleansing procedure, must be included in the letter in case a person reads only the invitation/result letter and not the leaflet **(VI - A)**.

10.5.2 When FOBT is used for screening: content of letters and leaflets

10.5.2.1 FOBT invitation letter

The letter inviting patients to perform FOBT screening should contain the following information:

- **Screening information:**

  o The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating);

  o Who the test is for (target population, age group); and

- o   The screening interval.

- **Organisational information:**

  - o   How to make and change the appointment when an appointment is required to pick-up the test;

  - o   Cost of the test (free or not); and

  - o   Where further information can be obtained (information services, telephone hotlines, patient groups, websites, etc.).

- **Information about the the screening test:**

  - o   Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);

  - o   How to obtain the result (mentioning the approximate waiting times); and

  - o   The proportion of people who may require further testing.

- **Information about the benefits of screening:** Emphasise that early detection can save lives.

- **Information about the harms/side effects/disadvantages of screening:**

  - o   Meaning of a FOBT positive result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy (see Chapter 5 for details), referring to colonoscopy leaflet; and

  - o   Fear/anxiety about cancer and screening results.

- **Information about the FOBT kit:**

  - o   Where to collect it; and

  - o   If the FOBT kit is sent with the letter, the letter should refer to the instruction leaflet and encourage participants to read it.

- **Referral to the invitation leaflet:** encouraging participants to read it.

10.5.2.2   FOBT invitation leaflet

The leaflet inviting patients to perform FOBT screening should contain the following information:

- **Screening information:**

  - o   The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating)

  - o   Who the test is for (target population, age group);

  - o   The screening interval;

  - o   Quality standards and quality assurance;

  - o   Other types of screening; and

  - o   Comments on people outside the recommended age group, including those at risk of colorectal cancer.

- **Colorectal cancer:**

  - o   Incidence;

  - o   Lifetime morbidity and mortality; and

  - o   Risk factors.

- **Screening test:**
    - o Nature (what is it?);
    - o Purpose (what the test is designed to measure);
    - o Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);
    - o Informed consent;
    - o How to obtain the result (mentioning the approximate waiting times);
    - o Meaning of the test results (What "negative", "positive" and "unclear" mean);
    - o Meaning of a FOBT positive result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy (see Chapter 5 for details), referring to colonoscopy leaflet;
    - o Mention the proportion of people who may require further testing; and
    - o Reassurance about follow-up.

- **Test characteristics:**
    - o False positive and false negative results (including chances of true positive, true negative, false positive, and false negative tests);
    - o Positive predictive value;
    - o Number needed to screen to prevent one death; and
    - o Reasons why FOBT sometimes need to be repeated.

- **Benefits of screening:**
    - o Mention that early detection can save lives;
    - o Cancer can be found earlier/be prevented; and
    - o Screening relieves fear and anxiety about cancer; peace of mind.

- **Harms/side effects/disadvantages of screening:**
    - o Harms/side effects/disadvantages of colonoscopy if follow-up is required: sedation, cleansing procedure, possible complications, discomfort and pain during the colonoscopy procedure;
    - o Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis; and
    - o Fear/anxiety about cancer and screening results.

- **Options:**
    - o Include deciding on having a colonoscopy or not (describe the natural course taken by the disease if not detected) or being not clear about what to decide (methods for clarifying and expressing values); and
    - o The opportunity to request to withdraw from the programme.

Guidelines on presenting probabilities of outcomes in an unbiased and understandable way (IPDAS, NHSBSP no. 65, p. 5):

- Use event rates specifying the population and time period;
- Compare outcome probabilities using the same denominator, time period, scale;
- Describe uncertainty around probabilities;
- Absolute risk should be used in preference to relative risk;
- Use visual diagrams;
- Use multiple methods to give probabilities (words, numbers, diagrams);

- Allow the patient to select a way of viewing probabilities (words, numbers, diagrams);

- Allow patient to view probabilities based on their own situation (e.g. age); and

- Place probabilities in context of other events.

10.5.2.3 FOBT result/follow-up letter

The letter to inform patients about FOBT screening result should contain the following information:

- The letter should be personalised with the name of the patient and give the FOBT screening test result.

- If the result is negative, its meaning should be explained in terms of the likelihood of having CRC and the possibility of false negatives. The screening interval should be also specified.

- If the test is unclear, its meaning should be explained. If the directives of the screening programme are to repeat the FOBT, the letter should mention it and the patient should be invited to perform a repeat test.

- If the test is positive, its meaning should be explained in terms of the likelihood of having CRC and possibility of false positive. The letter should refer to the colonoscopy leaflet sent with the letter that describes in detail the colonoscopy procedure and should encourage participants to read it. However, certain basic and practical information about the colonoscopy procedure, its harms and benefits, and logistic/organisational information relating to the colonoscopy appointment must be included in the letter in case a person reads just the letter and not the colonoscopy leaflet.

10.5.2.4 Colonoscopy leaflet (see Section 10.5.3.2)

10.5.3 When flexible sigmoidoscopy (FS) or colonoscopy is used for screening, either as primary screening test (FS or CS) or to follow-up a positive FOBT result (only CS): content of letters and leaflets

10.5.3.1 Endoscopy invitation letter

The letter inviting patients to perform endoscopy screening should contain the following information:

- **Screening information:**
  o The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating);
  o Who the test is for (target population, age group); and
  o The screening interval.

- **Organisational information:**
  o How to make and change the appointment;
  o Cost of the test (free or not); and
  o Where further information can be obtained (information services, telephone hotlines, patient groups, web sites, etc...).

- **Information about the screening test:**
  - o Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);
  - o How to obtain the result (mentioning the approximate waiting times); and
  - o Mention the proportion of people who may require further testing.
- **Information about benefits of screening:** Early detection can save lives.
- **Information about harms/side effects/disadvantages of endoscopy screening (see Chapter 5 for details):**
  - o For both FS (if colonoscopy is used as follow-up procedure) and colonoscopy: The possible complications of colonoscopy and discomfort and pain during the procedure;
  - o The meaning of a positive FS result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy, referring to colonoscopy leaflet; and
  - o Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis.
- **Information about the cleansing procedure.**
- **Referral to the endoscopy leaflet** encouraging participants to read it.
- **Options:**
  - o Include deciding whether to have an endoscopy (describe the natural course without having the endoscopy), or being not clear about what to decide (methods for clarifying and expressing values); and
  - o The possibility to withdraw consent at any stage (Chapter 5 recommendation).

10.5.3.2 Endoscopy invitation leaflet: example for colonoscopy

The leaflet to inform patients about a colonoscopy screening, either for primary screening or as follow-up after a positive FOBT or FS, should contain the following information:

- **Colorectal cancer and colorectal screening:**
  - o The purpose and the importance of screening; what early detection means;
  - o A description of colorectal cancer disease; and
  - o General information about the CRC screening programme.
- **In cases where colonoscopy is used as follow-up after a positive FOBT result or FS:**
  - o Explain why colonoscopy is required;
  - o How to interpret a FS positive result; and
  - o How to interpret a FOBT positive result: What "positive FOBT" result means: including chances of true positive, true negative, false positive and false negative test.
- **Colonoscopy procedure:**
  - o Nature (what is it?);
  - o Who the test is for; validity;
  - o Purpose (what the test is designed to measure, why it is being done);
  - o How to make and change an appointment;
  - o How the test is carried out;
  - o How to prepare for the colonoscopy (including bowel cleansing and options for sedation);

o   Who performs the test, where it is performed;

o   How long it takes;

o   What to do when the test is done;

o   Cost of the procedure: free or not;

o   How to obtain the result (approximate waiting times);

o   Meaning of colonoscopy results (normal, polyps, cancer);

o   Quality control of the colonoscopy procedure; and

o   What to do if people have symptoms after colonoscopy.

- **Positive outcomes:** Cancers can be found earlier/be prevented.

- **Harms/side effects/disadvantages of colonoscopy (see Chapter 5 for details):**

o   Associated restrictions on travelling or making important decisions due to sedation;

o   Cleansing procedure;

o   Possible adverse events including discomfort, pain and complications;

o   Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis;

o   Fear/anxiety about cancer and colonoscopy results; and

o   What support may be needed after the procedure, particularly if the patient is sedated.

- **Options:**

o   Include deciding on having a colonoscopy or not (describe the natural course without having the colonoscopy), or being not clear about what to decide (methods for clarifying and expressing values)

o   The opportunity to withdraw consent at any stage (Chapter 5 recommendation)

Guidelines on how to present probabilities of outcomes in an unbiased and understandable way (IPDAS, NHSBSP no65 p5) as described above for the invitation leaflet.

10.5.3.3   Endoscopy results/follow-up letter

The letter should be personalised with the name of the patient and give the endoscopy screening test result:

- If the result is negative, its meaning should be explained in terms of the likelihood of having CRC and possibility of false negatives. The screening interval should be also specified;

- If the test is positive, the letter should describe in detail what following steps to take.

10.6   Stylistic advice

The way information is presented plays an important role in determining its comprehension and acceptance. For this reason, it is essential that written information be guided by good communication principles in order to be easy to read and understood by the users.

Written information material should be clear, visually appealing and motivating to the intended audience.

Some recommendations on language, on text style and wording, and formatting are provided hereafter, based on the recent EU guidelines for quality assurance in cervical cancer screening (European Cancer Network 2008). They should be carefully considered by the screening staff to make the communication more effective and easily understandable to participants.

Recommendations

The language, text style, wording and formatting used in written information should follow these suggestions:

- **Language:**
  - Clear (about the topic: clarify points with examples);
  - Honest, respectful, polite;
  - Simple everyday language (no technical terms, jargon, abbreviations and acronyms);
  - Informal (use of pronouns like "we" and "you" to personalise the text);
  - Impartial;
  - Not top-down (no prescriptive style or paternalistic tone); and
  - Written in the active voice.

- **Text style and wording:**
  - Credible, reliable (indicating the source of information);
  - Up-to-date and contemporary;
  - Friendly and sympathetic;
  - Positively framed (e.g. 9 out of 10 recalled patients are found to be normal rather than 1 out of 10 recalled women will have cancer); and
  - Positive tone (alarming statements should be avoided).

- **Text format:**
  - Preferably plain layout;
  - Short sentences and brief paragraphs;
  - Use of diagrams and pictures;
  - Use of titles and subtitles (to distinguish different areas);
  - Bold or capital letters (to underline important points);
  - Larger print (essential for older target populations);
  - Use of white spaces (to facilitate reading);
  - Preferably question/answer and paragraph formats;
  - Appropriate colours (as some colours are difficult for colour-blind people to read); and
  - Logo.

10.7 Evaluating the quality of public information materials: are these materials meeting the required standard for quality?

There are currently different guides to assess the quality of communications tools. The International Patient Decision Aid Standard (IPDAS) collaboration group (an international group of more than 100 researchers, practitioners and stakeholders) has provided a framework of quality criteria for patient decisions aids used for screening or health decisions (Elwyn et al. 2006). Even if the IPDAS checklist does not address CRC screening specifically, it is a good guideline for evaluating the quality of communication tools produced by CRC screening programmes. This is the reason why we recommend using it.

The IPDAS framework, a list of 80 items, was produced as a consensus of the IPDAS group and developed based on evidence where it exists and the view of IPDAS experts. These criteria "might be considered to represent an ideal construction that may be difficult to attain. ....The criteria are not meant to be prescriptive." (Elwyn et al. 2006). The criteria (in *Developing a quality criteria framework for patient decision aids: online international Delphi consensus process* and IPDAS criteria checklist) address 3 domains of quality: the content (specific to the health condition and therapeutic/screening options), the development process (referring to the way the decision aid should be developed and relevant to any decision aid) and the effectiveness (relevant to any decision aid, to evaluate the effectiveness of the decision aid). Based on these criteria, a new instrument has been developed to assess the quality of decision support materials: the IPDASi assessment service (http://www.ipdasi.org/) which is currently undertaking a validation study assessing 30 decision support technologies.

10.8   References

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Electronic link to Appendix 1 - Click here*

*The above link leads to the corresponding chapter in Appendix 1 - Systematic evidence review -

Appendix 1 contains additional information on the literature search and analysis performed for key clinical questions examined during the preparation of the Guidelines.

Appendix 1

Systematic evidence review:
Summary documents and evidence tables for key clinical questions compiled for the European guidelines for quality assurance in colorectal cancer screening and diagnosis - First edition

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List of key clinical questions

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1

Introduction
EVIDENCE

EU CRC Guidelines Literature Group

1.1 Effectiveness of FOBT screening

1.1.1 Summary document

Silvia Minozzi and Jo Watson

CLINICAL QUESTION 1

Is FOBT screening offered to general population aged 50 and older effective in reducing colorectal cancer mortality and overall mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: FOBT screening test
C: No screening
O: Colorectal mortality, overall mortality after at least 5 (10) years of follow up
S: RCTs, systematic reviews of RCTs

SEARCH METHOD

In the first instance systematic reviews of randomised controlled studies have been searched. Search of primary RCTs was limited to those studies published after the last search date of the most recently published systematic review.

Quality assessment of systematic reviews was done using a simplified version of the QUOROM Statement checklist.

SEARCH METHOD

Medline: Search date 15th October 2007
Search Terms:
(("Colorectal Neoplasms"[Mesh]) AND ("Mass Screening"[Mesh]) AND ("Occult Blood"[Mesh]))
Systematic reviews only (no date restriction) – 42 results – most recent review (Kerr et al.) and Cochrane review (Hewitson et al.) selected for guideline evidence.
2007 only – 39 results – no relevant articles published after Kerr et al. Systematic review

Embase: Search date 15th October 2007
Search Terms:
(exp Mass Screening AND exp Large Intestine Tumour AND exp Occult Blood) AND (systematic review$ OR metaanalys$ OR meta-analys$) – 8 results – most recent from 2005, i.e. before Kerr et al. and therefore not included
 (exp Mass Screening AND exp Large Intestine Tumour AND exp Occult Blood) limit to yr="2007"
47 results – no relevant articles published after Kerr et al. systematic review
In December 2008 we also update our MedLine search using the following search strategy:

("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac)

RESULTS

Seven systematic reviews published between 1997 and 2007 have been retrieved. (1-7) The most up to date bibliographic search reported by the reviews includes studies published in 2006. One systematic review (Pignone 2002) was subsequently updated in 2008 (8) but we did not include this update as no relevant data regarding G-FOBT efficacy were reported. Three (1-3) out of the retrieved systematic reviews reported a meta-analysis and were included in this summary. All the reviews include randomised controlled trials which compare FOBT screening with no screening. For one of the trials included in the systematic reviews a subsequent update has been recently published and data were included in this summary. (9)

The methodological quality of the retrieved reviews was good. Two reviews searched on many databases (1,2) and the Cochrane review (1) also searched for unpublished trials. The assessment of the methodological quality of primary studies was performed in all the reviews, but the criteria were fully described only in the Cochrane review.

Only three studies are included in all the reviews. Kerr included one study which was excluded by the Cochrane review because it assesses the efficacy of only one screening round. The Cochrane review included one study not considered by Kerr. Heresbach also reported data from a French controlled trial.

The results of the reviews are in any case similar.

The Cochrane review (1) combines the results of the four studies and calculates the RR with 95% confidence interval; all the studies assess the efficacy of the guaiac test; three out of the four primary studies used an intention to screen analysis, this is not specifically stated for the fourth study.

Colorectal cancer mortality: annual and biennial screening considered together (4 studies, 329.642 participants): RR: 0.84 (CI95%0.78 -0.90). Only biennial screening considered: (3 studies, 245.764 participants): RR: 0.85 (CI95% 0.78 – 0.92).

Kerr (2) combines the results of three studies, the same considered by the Cochrane review, which assess the efficacy of the guaiac test:

Colorectal cancer mortality: annual and biennial screening considered together: RR 0.85 (CI95%0.79-0.93).

Colorectal cancer mortality: only one screening round, follow up 8 years, Immunochemical test (one study, 192.261 participants): RR: 0.68 (95%CI: 0.54-0.87).

Heresbach et al.(3) analysed colorectal cancer mortality and incidence data according to different screening programme durations. A meta-analysis of mortality results showed that subjects allocated to screening had a reduction of CRC mortality during a 10-year period (RR 0.86; CI 0.79–0.94) although CRC mortality was neither decreased during the 5–7 years after the 10-year (six rounds) screening period, nor in the last phase (8–16 years after the onset of screening) of a long-term (16 years or nine rounds) biennial screening. In other words, biennial FOBT decreased CRC mortality by 14% when performed over 10 years, without evidence-based benefit on CRC mortality when performed over a longer period.

In the last follow up of the Goteborg trial (9) after a mean of 9 years from the last screening, a 16% significant reduction in colorectal cancer mortality in the screening group compared with the control group was observed. The overall risk ratio of death from colorectal cancer was 0.84 (95% CI 0.71 to 0.99). The groups did not differ in incidence of colorectal cancer or in mortality for any causes.

CONCLUSIONS

There is good evidence that FOBT screening using the Guaiac test reduces mortality for colorectal cancer of invited participants by 16%. The reduction in colorectal cancer mortality has no impact on overall mortality because colorectal cancer is a disease which causes only a small proportion of the overall mortality. (LEVEL OF EVIDENCE I)

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1.1.2 Evidence tables

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Hewitson P, 2007	FOBT (hemoccult) annually or biennially vs. no screening	Meta-analysis of RCTs	4 studies with 329.642 adults (45-80 years old) at average risk of colorectal cancer Country: Denmark, Sweden, USA, UK	Primary outcomes: Colorectal cancer mortality (intention to screen result) Secondary outcomes: Sensitivity, attendance to screening, colorectal cancer incidence and stages, all cause mortality; harms of colonoscopy or sigmoidoscopy	From 8.5 to 18.4 years	Colorectal cancer mortality (4 studies) RR:0.84 (CI95%0.78 -0.90) Colorectal cancer mortality;biennial screening; (3 studies): RR: 0.85 (CI95% 0.78 – 0.92) Attendance: at least one round attended: 60% to 78% All cause mortality: (4 trials): RR: 1.00 (CI95% 0.99-1.02)	I

SR FOBT SCREENING – Hewitson 2007

Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	Medline, Embase, Cinhal, Psychinfo, Amed, Sigle, HMIC database, Cochrane library; reference list of retrieved articles; contact with authors; studies included in the previous Cochrane review
	Date restriction	From 1989 to February 2006
	any restriction	No language restriction
Selection	Inclusion and exclusion criteria	RCTs; adults at average risk of colorectal cancer; FOBT annually or biennially (on more than one occasion) vs. no screening; colorectal cancer mortality
Validity assessment	Criteria and process used	Allocation concealment; randomisation method
Data abstraction	Process used	Independently by two reviewers with standardized forms
Quantitative data synthesis	Measures of effect, method of combining results	RR, Peto Odds Ratio; meta-analysis using fixed and random effect model; test of heterogeneity; Data analysed according to the intention to screen.
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	no
	summary results	Yes (meta-analysis performed)

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Kerr 2007	FOBT vs. no screening	Meta-analysis of RCTs	4 RCTs Participants aged from >=30 to 80 years Country: USA, UK, Denmark, Japan	CRC mortality CRC incidence	From 2 years to 18 years	CRC mortality – Guaiac FOBT: 0.85 (95%CI: 0.79-0.92) from 3 trials CRC mortality – Immunochemical FOBT: 0.68 (95%CI: 0.54-0.87) from 1 trial CRC incidence – FS and FOBT combined vs. FOBT alone: 3.6 per 1000 vs. 5.9 per 1000 (p=0.24)	I

SR FOBT SCREENING 2 – Kerr 2007

Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	Medline, Embase, Current Contents, and the Cochrane Library. DARE and Health Technology Assessment databases, clinical trial and guideline resources, and references from retrieved publications.
	Date restriction	Jan 1997 to Nov 2004
	any restriction	Language restrictions not mentioned
Selection	Inclusion and exclusion criteria	Full reports from RCTs comparing FOBT screening to no screening (or FOBT and FS to FOBT only)
Validity assessment	Criteria and process used	Data relevant to study quality and statistical precision were abstracted using relevant checklists
Data abstraction	Process used	Not given (may be included in the associated NZHTA report)
Quantitative data synthesis	Measures of effect, method of combining results	RR: Meta-analysis using a fixed effects model
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	?
	summary results	Yes (Meta-analysis performed)

Author, publication year	Intervention	Study design	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Heresbach 2006	Biennial FOBT	Systematic review of faecal occult blood test screening studies (RCT and CT)	10 RCTs were included: publication of four prospective screening programmes in the USA, UK Denmark, and France	Risk of death from CRC CRC incidence Short-term time (5–6 No. rounds during period 8–10 yrs duration) Long-term time (6–9 No. rounds during period 10–16 yrs duration)	*CRC mortality RR (95% CI)* Short-term time: 0.86 (0.79–0.94) Long-term time: 0.88 (0.81–0.95) *CRC incidence RR (95% CI)* Short-term time: 1.01 (0.95–1.06) Long-term time: 1.01 (0.96–1.06)	I The combined relative risk estimate for short-term, long-term described a significant decrease in CRC mortality of 14–15%. Biennial FOBT decreased CRC mortality by 14% when performed over 10 years, without evidence-based benefit on CRC mortality when performed over a longer period.

SR FOBT SCREENING 3 – Heresbach 2006

Quality of reporting (QUOROM CHECKLIST)

Methods search	Databases , register, hand searching;	MEDLINE search contact with authors ad expert in the field
	Date restriction	Date not reported
	Any restriction	-
Selection	Inclusion and exclusion criteria	
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Papers and trials were selected for the meta-analysis when they met the following criteria: experimental study with CRC mortality or incidence as the main follow-up criteria, a 10-year follow-up at least, a relative risk reported with a 95% CI and a relative risk from CRC death reported for biennial FOBT screening based on the guaiac test.
Quantitative data synthesis	Measures of effect, method of combining results	fixed-effect model was used unless the test of heterogeneity gave a P value less than 0.1. In such a case the random effect method has been used.
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	Narrative and tabulated study description
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Briefly reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	Reported

Author, publication year	Study design Study objective	Intervention	Participants	Outcomes	Follow up	Results	Level of evidence
Lindholm 2008 Last Update of the Goteborg trial	RCT to evaluate the effect of faecal occult blood test (FOBT) screening on colorectal cancer (CRC) mortality	Screening group: rehydrated Hemoccult-II (two to three times) Control group: no screening Subjects with a positive test result were offered sigmoidoscopy and a double-contrast enema	68,308 citizens aged of 60–64 years. screening group: 34144 control group: 34164. Goteborg, Sweden	Primary: death from colorectal cancer	Mean follow-up time of 15 years and 6 months (range 11 years and 3 months to 19 years and 5 months in the various cohorts) from the first invitation, and 8 years and 8 months (range 6 years and 7 months to 13 years and 5 months) from the last screening occasion 9 years after screening	*Positive FOBT* Prevalence screening: 801 (3.8%) First re-screening: 846 (4,2%) Second re-screening: 533 (4,4%) Total: 2180 (4.1%) *incidence of colorectal cancer after 19 years (per 1000 person-years)* screening group: 1.53 control group: 1.60 incidence ratio: 0.96 (95% CI 0.86 to 1·06) *colorectal cancer mortality (per 1000 person-years)* screening group: 0.53 control group: 0.64 OR 0.84 (95% CI 0.71 to 0.99) *Death for all causes (per 1000 person-years)* Screening group: 22.48 Control group: 22.10 OR: 1.02 (95% CI 0.99 to 1.06)	**II** A significant 16% reduction in mortality from colorectal cancer 19 years after the start of the screening programme was observed. The sample was population based and restricted only for age. The external validity of the study is high.

Quality assessment: Random allocation of individuals of Goteborg born between 1918 and 1931 (3 cohorts depending on time of birth; 1918-1922, 1923-1927 and 1928-1931 (age was the only inclusion criteria); randomisation is not described in this publication but both sequence generation and concealment of allocation reported in the previous publication of this trial were considered adequate. Compliance to screening: 70% (23 916 individuals). Intention-to-screen analysis. Outcome assessment performed through register analysis blindly with regard to study group.

1.2 Test performance characteristics (sensitivity and specificity) of immunochemical FOBT vs. guaiac FOBT

1.2.1 Summary document

Rita Banzi

CLINICAL QUESTION 2

Is immunochemical FOBT (I-FOBT) superior to guaiac FOBT (G-FOBT) in its test performance characteristics (sensitivity and specificity)?

PICOS

P: Asymptomatic population
I: I-FOBT
C: G-FOBT
O: 1. Sensitivity / CRC detection rate, 2. Specificity for the detection of colorectal cancer or advanced adenoma
S: (Systematic reviews of) diagnostic accuracy studies, RCTs, (preference will be given to prospective diagnostic accuracy study where patients are consecutively recruited from a clinical setting)

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic. We also performed a literature search on a MedLine and Cochrane Library with the following key words:

Medline: ("mass screening " Mesh OR screen*) AND ("Colonic neoplasms Mesh OR "colorectal neoplasms " Mesh OR "COLONIC POLYPS" Mesh OR colonic neoplasms* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasms* OR colon polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood Mesh OR guaiac) AND immunochemical
Limits: humans, English, French, Italian, Spanish

RESULTS

We analysed six screening population studies on colorectal cancer comparing different commercially available G-FOBT and I-FOBT. (1-6) All the programmes recruited an asymptomatic population older than 50 years (with the exception of Castiglione 2006 who recruited population older than 40 years) at average or unknown risk of colorectal cancer. The primary objective of the studies was the prospective evaluation of the performance characteristics of the two tests (sensitivity, specificity, predictive value). Two studies assessed also the improvement in screening accuracy of the combination of I-FOBT and G-FOBT. In two studies (1,6) as the confirmatory diagnostic procedure (colono-

scopy) was restricted to subjects classified as positive on at least one of the tests, the specificity of each test could only be estimated, and the possibility of verification bias can not be excluded. All but one (4) are prospective studies conducted with the general population at average risk of colorectal cancer.

A head-to-head comparison of relative performances of a sensitive G-FOBT (Hemoccult Sensa) with a brush-sampling I-FOBT (InSure) demonstrated that I-FOBT was significantly more sensitive for detecting cancer (75% vs. 37.5%) and adenomas (27% vs. 15%). Specificity for neoplasia, estimated from the false-positive rate, was 96.6% for InSure and 97.5% for Hemoccult Sensa. Specificity for any pathology was 98.8% and 98.7%, respectively. (1)

Two studies were conducted in the US and they evaluated a sensitive G-FOBT test (Hemoccult Sensa), an I-FOBT (FlexSure OBT or Hemeselect), and their combination in two large screening populations (5,932 and 8,104 respectively). (2, 5) Patients who tested positive using any FOBT test were recommended by the study staff to undergo further clinical examination, preferably colonoscopy. The sensitivity and the specificity of Hemoccult Sensa test for detecting colorectal carcinoma and advanced colorectal adenoma was lower than that of the FlexSure OBT but higher than the Hemeselect test. The likelihood ratio, which is a more accurate reflection of how likely it is that a person with colorectal cancer will be test positive, showed that the I-FOBT and the combination test detected distal colorectal cancer more effectively than distal colorectal adenoma. One study reported that an increase of testing performance could be achieved by confirming the G-FOBT (Hemoccult II Sensa test, more sensitive) using a positive result on I-FOBT (Hemeselect, more specific). (2)

Two large population screening studies were conducted in Italy involving almost 50,000 people. (3, 4) Results from the first study allowed the estimation of the relative sensitivity of G-FOBT (Hemoccult) vs. I-FOBT (Hemeselect) that was 88.2% (p<0.05). Specificity for cancer was slightly higher with I-FOBT 96.7% (CI 95% 96.2-97.2) than with G-FOBT 93.3% (CI 95% 92.6-94.0). (3) The largest screening study conducted between 1992 and 1997 estimated the sensitivity over a 2-year period, by the proportional incidence method; It was higher for I-FOBT (RPHA) than for G-FOBT (82% versus 50%, respectively; p<0.01). (4)

Similar results were obtained in a large population screening programme in France (n=10673) which in addition compared accuracy of I-FOBT using different haemoglobin cut-off points. Using the usual cut-off point of 20 ng/ml haemoglobin, the gain in sensitivity associated with the use of I-FOBT (50% increase for cancer and 256% increase for high risk adenoma) was balanced by a decrease in specificity. The number of extra false positive results associated with the detection of one extra advanced neoplasia (cancer or high risk adenoma) was 2.17 (95% confidence interval 1.65-2.85). With a threshold of 50 ng/ml, I-FOBT detected more than twice as many advanced neoplasias as the G-FOBT (ratio of sensitivity = 2.33) without any loss in specificity (ratio of false positive rate = 0.99). With a threshold of 75 ng/ml, associated with a positivity rate similar to G-FOBT (2.4%), the use of I-FOBT allowed a gain in sensitivity of 90% and a decrease in the false positive rate of 33% for advanced neoplasia. (6)

From the literature search we retrieved seven additional studies: one RCT, (7) one cohort study (8) and five diagnostic accuracy studies. (9-13)

Within a population based study on a sample of 20,623 individuals 50–75 years of age, patients were randomised to either G-FOBT (Hemoccult-II) or I-FOBT (OC-Sensor). The positivity rate difference was 3.1% (p <0 .01). Cancer and advanced adenomas were found, respectively, in 11 and 48 of G-FOBTs and in 24 and 121 of I-FOBTs. Differences in positive predictive value for cancer and advanced adenomas and cancer were, respectively, 2.1% (p=0.04) and -3.6% (p=0.05).

A small difference in specificity between G-FOBT and I-FOBT was found in favour of G-FOBT (2.3% (p <0.01) and -1.3% (p <0.01) while the detection rates for advanced adenomas and cancer were significantly higher for I-FOBT (0.1% (p <0 .05) and 0.9% (p<0.01)). The number to scope to find 1 CRC is not different between G-FOBT and I-FOBT.

Few differences between the guaiac-based and immunochemical- based tests in terms of completion rate, positivity rate, or positive predictive values for adenomatous polyps or colorectal cancer were noted in an American cohort study in which almost 6 000 patients of different firms were screened with different tests. (8)

However in four out of the five diagnostic accuracy studies I-FOBT was found more specific and appears to be more accurate than the G-FOBT for the detection of significant colorectal neoplasia. (9-12). Higher positivity rates for immunochemical FOBT did not translate into higher false-positive rates, and both test types resulted in a high yield of neoplasia (12). In the follow up evaluation of the Burgundy cohort the I-FOBT was superior to the G-FOBT for the detection of both cancers and adenomas: the number of detected cancers was 2.6 times higher with the I-FOBT than with the G-FOBT, and the number of advanced adenomas 3.5 times higher. (11)

Finally, Rozen et al. found that on 1,410 consecutive persons attending a CRC screening/follow-up service or in symptomatic patients presenting for evaluation of abdominal complaints a guaiac test, which does not require dietary restrictions, was significantly more sensitive for any colorectal neoplasm than the immunochemical FS. They conclude that the lower specificity is still acceptable for a population screening. (13)

CONCLUSIONS

Although the analysed population screening used different commercially available tests and slightly different protocols, the results of all studies consistently showed that I-FOBT is significantly better as a "first step" in the screening of colorectal cancer and adenomas when compared with traditional and highly sensitive G-FOBT tests. The relevance of benefits is primarily due to a gain in the estimated sensitivity and specificity. (LEVEL OF EVIDENCE III)

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1.2.2 Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results*	Level of evidence Conclusions
Smith 2006	Immunochemical FOBT (InSure); guaiac FOBT (Hemoccult II Sensa) Reference standard: colonoscopy for positives, nothing for negatives	Diagnostic cross-sectional study with prospective recruitment	<u>Screening population</u>: asymptomatic general population at unknown risk of CRC aged 50-75; N:2351 <u>Diagnostic population</u>: patients with symptoms that raise the possibility of a diagnosis of CRC recruited before they proceeded to diagnostic colonoscopy or surgery N: 161 Australia	True-positive rates, false-positive rates, specificity, sensitivity, positive predictive value	<u>True positive rate</u>: total cancer InSure 82.4% (CI 95% not reported); Hemoccult II Sensa 47.1% (CI 95% not reported) Significant adenoma InSure 44.4% (CI 95% not reported); Hemoccult II Sensa 24.2% (CI 95% not reported) <u>False positivity rates**</u>: InSure 1.2% (CI 95% not reported); Hemoccult II Sensa 1.3% (CI 95% not reported) <u>Specificity**</u>: InSure 98.8% (CI 95% not reported); Hemoccult II Sensa 98.7% (CI 95% not reported) <u>Sensitivity</u>: total cancer InSure 75% (CI 95% not reported); Hemoccult II Sensa 37.5% (CI 95% not reported) Significant adenoma InSure 27% (CI 95% not reported); Hemoccult II Sensa 15% (CI 95% not reported) <u>Positive predictive value for all neoplasia**</u>: InSure 41.9% (CI 95% not reported); Hemoccult II Sensa 40.4 % (CI 95% not reported)	**III** I-FOBT (specifically InSure) was better than a sensitive G-FOBT at detecting colorectal cancer (any stage) and advanced adenomas

*screening population

** for all neoplasia

Participants representative of people which could receive the test in clinical practice (screening population).

Selection criteria clearly described.

Clear description of index tests and reference standard.

Reference standard: colonoscopy of positives, nothing for negatives. Authors underline that specificity could not be calculated because of the lack of reference standard for negatives but only deducted form the false positive rates (1-false positive rate).

Blind assessment of results of index test: yes; Blind assessment of reference standard; Number of subjects lost at follow up reported: yes.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Allison 1996	1. Immuno-chemical FOBT (Hemeselect). 2. Guaiac FOBT (Hemoccult II, Hemoccult II Sensa) 3. Hemoccult II Sensa and Hemeselect combination Reference test: colonoscopy for positives, two year follow up for negatives	Diagnostic cross-sectional study with prospective recruitment	Asymptomatic population at average risk involved in CRC screening programme, older than 50 (30.2% age 50-59 yrs, 39.0% age 60-69; 30.8% older than 70). N:8104 California	Sensitivity, specificity, and predictive value	*Carcinoma* Sensitivity: Hemoccult II 37.1% (CI 95% 19.7-54.6) Hemoccult II Sensa 79.4% (CI 95% 64.3-94.5) Hemeselect 68.8% (CI 95% 51.1-86.4) Combination 65.6% (CI 95% 47.6-83.6) Specificity: Hemoccult II 97.7% (CI 95% 97.3-98) Hemoccult II Sensa 86.7% (CI 95% 85.9-87.4) Hemeselect 94.4% (CI 95% 93.8-94.9) Combination 97.3% (CI 95% 96.9-97.6) Positive predictive value: Hemoccult II 6.6% (CI 95% 3.7-11.2) Hemoccult II Sensa 2.5% (CI 95% 1.7-3.7) Hemeselect 5.0% (CI 95% 3.2-7.6) Combination 9.0% (CI 95% 5.8-13.6) *Polyp* Sensitivity: Hemoccult II 30.8% (CI 95% 21.6-40.1) Hemoccult II Sensa 68.6% (CI 95% 59.2-77.9) Hemeselect 66.7% (CI 95% 57.0-76.3) Combination 50.0% (CI 95% 39.8-60.2) Specificity: Hemoccult II 98.1% (CI 95% 97.7-98.4) Hemoccult II Sensa 85.7% (CI 95% 86.7-88.2) Hemeselect 95.2% (CI 95% 94.7-95.7) Combination 97.9% (CI 95% 97.6-98.2) Positive predictive value: Hemoccult II 16.7% (CI 95% 11.9-22.8) Hemoccult II Sensa 6.7% (CI 95% 5.3-8.4) Hemeselect 15.5% (CI 95% 12.3-19.3) Combination 21.9% (CI 95% 16.9-27.9) Detection rate: Hemoccult II 1.6/1000 cancer; 4.1/1000 polyps Hemoccult II Sensa would find 1.8/1000 more CRC and 5.0/1000 more polyps than Hemoccult II and 111 more colonoscopies would be needed. Hemeselect would find 1.3/1000 more carcinomas and 5.0/1000 more polyps and 34 more colonoscopies would be needed. The combination test would find 1.1/1000 more cancer and 2.4/1000 more polyps and 5 more colonoscopies would be needed.	III HemeSelect and a combination test in which HemeSelect is used to confirm positive Hemoccult II Sensa results improve on Hemoccult II in screening patients for colorectal cancer.

Participants representative of people which could receive the test in clinical practice.

Selection criteria clearly described.

Reference standard: medical records of positive patients to obtain information on follow up and colonoscopy, two years follow up for negatives with inspection of medical records, with the assumption that all polyps or carcinomas present at the time of a negative test became clinically apparent within two years.

Clear description of index tests and reference standard.

Blind assessment of results of index test: yes.

Number of subjects lost at follow up reported: 4%.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Castiglione 1996	Immunochemical FOBT (Hemeselect); guaiac FOBT (Hemoccult) screening Reference standard: colonoscopy for positives, follow up with further test after two years	Diagnostic cross-sectional study with prospective recruitment	Asymptomatic population at average risk involved in CRC screening programme, aged 40-70. N:8008 Italy	Positivity rates, positive predictive values (PPVs); specificity	Positivity rates: Hemoccult 6.0% (CI 95% 5.5-6.5); Hemeselect (+) 3.1% (CI 95% 2.7-3.4) PPV for cancer: Hemoccult 3.7% (CI 95% 1.9-5.6); Hemeselect (+) 8.4% (CI 95% 4.6-12.2) PPV for adenomas: Hemoccult 19.7% (CI 95% 15.8-23.6); Hemeselect (+) 30.5% (CI 95% 24.2-36.9) Specificity: Hemoccult 94.1% (CI 95% 93.6-94.6); Hemeselect (+) 97.1% (CI 95% 96.7-97.5) relative sensitivity: Hemoccult vs. Hemeselect 88.2% (p<0.05)	III Hemeselect is either as effective as Hemoccult with a significant improvement of specificity or significant more sensitivity than guaiac testing with a minor decrease in specificity according to the higher or lower positive threshold.

Participants representative of people who could receive the test in clinical practice.

Selection criteria clearly described.

Reference standard: results of diagnostic work up for positives (colonoscopy), two years follow up for negatives (people with negative test not undergoing to diagnostic work up in the following two years were considered true negatives.

Blind assessment of results of index test: yes.

Clear description of index tests and reference standard.

Number of subjects lost at follow up not reported.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Zappa 2001	Immunochemical FOBT (RPHA); Guaiac FOBT	Diagnnostic cross-sectional study with Retrospective rescruitment	Asymptomatic population involved in CRC screening programme, 50-70 yrs N:41774 Italy	Positivity rate, sensitivity, detection rate	Positivity rate: immunochemical FOBT (RPHA) 4.5% (CI 95% 4.2-4.8); guaiac FOBT_4.7% (CI 95% 4.4-5.0) Sensitivity*: immunochemical FOBT (RPHA) 82% (CI 95% 67-92); Guaiac FOBT 50% (CI 95% 34-63); Detection rate: Immunochemical FOBT (RPHA) DR: 3.5‰ (CI 95% 2.8-4.4); guaiac FOBT DR: 2.0‰ (CI 95% 1.6-2.4); The RPHA DR for cancer was significantly higher than that of guaiac at the first screening (4.5‰ versus 2.7‰; p<0.05) as well as at the repeat screening (2.7‰ versus 1.2‰; p<0.01).	III our study confirms that RPHA is more sensitive compared with the guaiac test

*2-year sensitivity estimated by the proportional incidence method.

Participants representative of people who could receive the test in clinical practice .

Selection criteria clearly described.

Clear description of index tests and reference standard.

Reference standard: clinical record of all patients followed for two years.

Blind assessment of results of index test: yes.

Number of subjects lost at follow up not reported.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Guittet 2007	Immunochemical FOBT (I-FOBT); Guaiac FOBT (non-rehydrated Hemoccult II test) Reference standard: colonoscopy for positives. Nothing for negatives	Diagnnostic cross-sectional study with prospective recrtuiment	Asymptomatic population involved in CRC screening programme, 50-74 yrs N:10673 France	Ratio of sensitivities (RSN); ratio of false positive rates (RFN); predictive positive value	RSN (I-FOBT/G-FOBT) = 1.50 for cancer RSN (I-FOBT/G-FOBT) = 3.56 for high risk adenomas The <u>sensitivity</u> of I-FOBT was higher than that of G-FOBT for cancer and for high risk adenoma. The gain in sensitivity associated with the use of I-FOBT (50% increase for cancer and 256% increase for high risk adenoma) was balanced by a decrease in specificity. <u>predictive positive value</u> of I-FOBT was lower than that of G-FOBT for cancer (4.0% vs. 7.3%) and similar for high risk adenomas (22% vs. 27%).	**III** I-FOBT tests have no dietary or medication restrictions. These tests have superior sensitivity and specificity, the gain being more important for high risk adenomas than for cancers.

Participants representative of people who could receive the test in clinical practice.

Selection criteria clearly described.

Reference standard: colonoscopy for positives; nothing for negatives; possible verification bias; in fact authors stated that as the confirmatory procedure (colonoscopy) was restricted to subjects classified as positive on at least one of the tests, the sensitivity and specificity of each test could not be directly estimated. We therefore compared the accuracy of both tests by calculating the ratio of sensitivities (RSN) and the ratio of false positive rates (RFP).

Clear description of index tests and reference standard.

Blind assessment of results of index test: yes.

Number of subjects lost at follow up reported: 20% of positives did not performed colonoscopy.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Van Rossum 2008	RCT	1. G-FOBT (Hemoccult-II) or 2. I-FOBT (OC-Sensor) Colonoscopy was offered to all FOBT-positive patients (Positives).	Random sample of 20,623 individuals 50–75 years of age, randomised to either G-FOBT (Hemoccult-II) or I-FOBT (OC-Sensor) mean age of the invited individuals was 60.7±7.1 years (mean±SD) more women in the invited population 3.4% (95% CI, 2.5– 4.4; p<0.01) but no differences in the allocated population June 2006 to February 2007 Nijmegen, Amsterdam	Positivity rate according to the to the per-protocol and to the intent-to-screen analysis (number of true positives relative to the number of invited persons) Number needed to screen to find 1 true positive Positive predictive value (PPV) Specificity	***Positive rate*** G-FOBT: 117/4836 (2.4%) I-FOBT: 339/6157 (5.5%) Difference: 3.1% (95% CI, 2.3–3.8; p<0.01) ***Complete follow-up of FOBT-positive patients (%,95%CI)*** G-FOBT: 88.0 (82.2–93.9) I-FOBT: 82.6 (78.6–86.6) Difference: -5.4 (-13.1 to 2.3)* ***Detection rate intention to screen*** <u>All polyps and cancer</u> G-FOBT: 0.8 (0.6–0.9) I-FOBT: 2.1 (1.8–2.4) Difference: 1.3 (1.0–1.7)* <u>All adenomas and cancer</u> G-FOBT: 0.7 (0.5–0.9) I-FOBT: 1.9 (1.7–2.2) Difference: 1.2 (0.9–1.6)* <u>All advanced adenomas and cancer</u> G-FOBT: 0.6 (0.4–0.7) I-FOBT: 1.4 (1.2–1.6) Difference: 0.9 (0.6–1.1)* <u>Cancer</u> G-FOBT: 0.1 (0.0–0.2) I-FOBT: 0.2 (0.1–0.3) Difference: 0.1 (0.0–0.2)* ***Detection rate per protocol*** <u>All polyps and cancer</u> G-FOBT: 1.7 (1.3–2.0) I-FOBT: 3.5 (3.1–4.0) Difference: 1.9 (1.3–2.5)* <u>All adenomas and cancer</u> G-FOBT: 1.5 (1.1–1.8) I-FOBT: 3.3 (2.8–3.7) Difference: 1.8 (1.2–2.4)*	II Direct comparison of the tests demonstrated a significantly higher participation rate for the I-FOBT. There is a small difference in specificity between G-FOBT and I-FOBT but the detection rates for advanced adenomas and cancer were significantly higher for I-FOBT. The number to scope to find 1 CRC is not different between G-FOBT and I-FOBT. G-FOBT significantly underestimates the prevalence of advanced adenomas and cancer in the screening population compared with I-FOBT.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
					All advanced adenomas and cancer G-FOBT: 1.2 (0.9–1.5) I-FOBT: 2.4 (2.0–2.7) Difference: 1.2 (0.7–1.7)* Cancer G-FOBT: 0.2 (0.1–0.4) I-FOBT: 0.4 (0.2–0.5) Difference: 0.2(0.0–0.4)* **Positive predictive value** All polyps and cancer G-FOBT: 77.7 (69.6–85.7) I-FOBT: 77.9 (73.0–82.7) Difference: 0.2 (-9.2 to 9.6) All adenomas and cancer G-FOBT: 69.9 (61.0–78.8) I-FOBT: 71.8 (66.5–77.1) Difference: 1.9 (-8.3 to 12.1) All advanced adenomas and cancer G-FOBT: 55.3 (45.7–64.9) I-FOBT: 51.8 (45.9–57.6) Difference: -3.6 (-14.8 to 7.7) Cancer G-FOBT: 10.7 (4.7–16.6) I-FOBT: 8.6 (5.3–11.9) Difference: -2.1 (-8.6 to 4.4) **Specificity** All advanced adenomas and cancer G-FOBT: 99.0 (98.8–99.3) I-FOBT: 97.8 (97.4–98.1) Difference: -1.3 (-1.8 to -0.8)* Cancer G-FOBT: 98.1 (97.7–98.5) I-FOBT: 95.8 (95.3–96.3) Difference: 2.3 (-2.9 to -1.6)*	

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
					Number needed to screen to find an advanced adenoma or carcinoma G-FOBT 181 I-FOBT 71 ***Number needed to screen to find 1 cancer*** G-FOBT 936 I-FOBT 430	

* p<0.05

Quality assessment: random samples were taken according to postal address and randomised to receive a G-FOBT or an I-FOBT (unclear allocation concealment; if more than 1 individual was listed at the same address they received the same test to ensure relative blinding to the alternative test (prevention against contamination); unit of allocation and analysis: patients; open design (no blinded outcome assessment); intention to screen and per protocol analysis; attrition: Participation rate was statistically significant different between groups (Difference: 12.7 (11.3–14.1); G-FOBT: 4836 46.9 (46.0–47.9), I-FOBT: 6157 59.6 (58.7–60.6).

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Ko 2003	Cohort study	1.Immunochemical FOBT (FlexSure OBT; SmithKline Diagnostics, Palo Alto, California) 2. Guaiac FOBT (Hemoccult SENSA; Beckman Coulter, Inc., Palo Alto, California) depending on the patient corresponding firm	I-FOBT: 2965 G-FOBT: 2964 mean age (±SD): 65.4±10.5 years; 98% were male. August 1, 2000, and September 30, 2001 Seattle campus of the VA Puget Sound Health Care System USA	Positive predictive value	***Positive result*** I-FOBT: 128 (9) G-FOBT: 122 (9) p=0.72 ***Colon exam completed among patients with positive results*** I-FOBT: 69 (54) G-FOBT: 64 (52) p=0.73 ***Positive predictive value*** <u>Any type of polyp</u> I-FOBT: 71 (49) G-FOBT: 68 (44) p=0.78 <u>Any adenoma or malignancy</u> I-FOBT: 58 (40) G-FOBT: 59 (38) p=0.87 <u>Adenoma >1 cm or malignancy</u> I-FOBT: 17 (12) G-FOBT: 30 (19) p=0.09 <u>Malignancy</u> I-FOBT: 7 (5) G-FOBT: 14 (9) p=0.18	**III** Few differences between the guaiac-based and immunochemical-based tests in terms of completion rate, positivity rate, or positive predictive values for adenomatous polyps or colorectal cancer.

Quality assessment: not clear whether the design is prospective or retrospective; population is representative of male; good comparability of the two cohorts, similar response rate to screening (about 50% of the invited persons returned the sample cards: 48% in the G-FOBT group, 48% in the I-FOBT group); outcome assessment through medical records (not blinded).

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Wong 2003	Prospective diagnostic accuracy study	1.Immunochemical FOBT (FlexSure OBT, FS) and 2. Guaiac FOBT (Hemoccult SENSA, HOS) Ref standard: colonoscopy to all patients	136 consecutive patients at who required colonoscopy for the investigation of gastrointestinal symptoms or colonic polyp surveillance mean age of 58 years (range, 38–90 years) and 58% were female Between October 2000 and May 2001 Queen Mary Hospital, Hong Kong, China	Sensitivity, specificity, Positive predictive value	*Overall positivity rate (n=135)* HOS: 56/135 (41%) FS: 19/135 (14%) p<0.0001 *Cancers detected* HOS: 9/9 (100%) FS: 8/9 (89%) *Large adenomas detected* HOS: 1/2 (50%) FS: 1/2 (50%) p=1.0 *Significant neoplasia detected* HOS: 10/11 (91%) FS: 9/11 (82%) p=1.0 *PPV for cancers* HOS: 9/56 (16%) FS: 8/19 (42%) p=0.028 *PPV for significant neoplasia* HOS: 10/56 (18%) FS: 9/19 (47%) p=0.016	**III** Conclusions: the immunochemical test FlexSure OBT is more specific and appears to be more accurate than the guaiac-based Hemoccult SENSA test for the detection of significant colorectal neoplasia in a Chinese population

Quality assessment: population is not representative of the average population (participants required colonoscopy for the investigation of gastrointestinal symptoms or colonic polyp surveillance); blinded assessment of outcome: all tests were developed and interpreted by a single experienced technician who was blind to the clinical diagnosis. Colonoscopy was performed without knowledge of the FOBT result.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Hoepffner 2006	Prospective diagnostic accuracy study	1. Guaiac-FOBT Hemoccult (Beckman Coulter, Inc., Fullerton, CA, USA) 2. Highly sensitive I-FOBT (Immundiagnostik AG, Bensheim, Germany, ELISA-IFOBT) 3. I-FOB test strip device (Prevent ID CC, bedside IFOBT) Ref standard: colonoscopy (all patients)	387 consecutive patients (237 who either had known clinical diagnosis (e.g. IBD) or were symptomatic suggestive of colonic disease and 150 healthy patients underwent CRC screening) median age: 51 years (range:5 to 96) 186 males and 201 females January 2002 to December 2004. Germany	Sensitivity, specificity, positive and negative predictive value (PPV and NPV)	***Sensitivity (%, CI 95%)*** <u>Adenoma</u> G-FOBT: 5.56 (0.14–27.29) bedside IFOBT: 18.9 (3.58–41.42) ELISA-IFOBT: 22.2* (6.41–47.64) <u>Cancer</u> G-FOBT: 37.0 (24.29–51.26) bedside IFOBT: 74.0* (60.35–85.04) ELISA-IFOBT: 77.7* (64.40–87.96) <u>Cancer + adenoma</u> G-FOBT: 29.1 (19.05–41.07) bedside IFOBT: 59.7* (47.50–71.12) ELISA-IFOBT: 63.8* (51.71–74.88) ***Specificity (%, CI 95%)*** <u>Cancer + adenoma</u> G-FOBT: 90.2 (84.64–94.32) bedside IFOBT: 94.5 (89.84–97.46) ELISA-IFOBT: 96.3* (92.21–98.65) ***PPV (%, CI 95%)*** <u>Adenoma</u> G-FOBT: 5.9 (0.15–28.69) bedside IFOBT: 25.0 (5.49–57.19) ELISA-IFOBT: 40.0 (12.16–73.76) <u>Cancer</u> G-FOBT: 55.6 (38.10–72.06) bedside IFOBT: 81.6 (67.98–91.24) ELISA-IFOBT: 87.5 (74.75–95.27) <u>Cancer + adenoma</u> G-FOBT: 56.7 (39.49–72.90) bedside IFOBT: 82.6 (69.67–91.77) ELISA-IFOBT: 88.4 (76.56–95.65)	**III** Conclusions: the new bedside IFOBT is more specific and appears to be more accurate than the Guaiac-based Hemoccult test for the detection of significant colonic bleeding lesions including CR neoplasia.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
					NPV (%, CI 95%) <u>Adenoma</u> G-FOBT: 89.7 (84.02–93.88) bedside IFOBT: 91.2 (85.86–94.98) ELISA-IFOBT: 91.9 (86.72–95.48) <u>Cancer</u> G-FOBT: 81.3 (74.89–86.70) bedside IFOBT: 91.7 (86.49–95.40) ELISA-IFOBT: 92.9 (87.99–96.30) <u>Cancer + adenoma</u> G-FOBT: 74.4 (67.72–80.28) bedside IFOBT: 84.2 (78.16–89.18) ELISA-IFOBT: 85.9 (79.99–90.56)	

Quality assessment: mixed population: patients who either had known clinical diagnosis (e.g. IBD) or were symptomatic suggestive of colonic disease and healthy patients underwent CRC screening.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Dancourt 2008	Prospective diagnostic accuracy study	1. Guaiac-FOBT Hemoccult (Hemoccult II; Beckman Coulter Inc, Fullerton CA, USA) 2. immunochemical I-FOBT (Instant-view, Alpha Scientific Designs, Poway, CA, USA) Ref standard: colonoscopy for positive	17,215 average risk individuals aged 50 to 74 Burgundy, France	Sensitivity, specificity, positive and negative predictive value (PPV and NPV)	*Positive rate to either or both tests* Overall: 1558 (9.0%) G-FOBT: 3.1% I-FOBT: 6.9% p<0.001 *Positive rate among the participants who screened positive and underwent a colonoscopy* (N=1205, 78.2%) G-FOBT: 76.2% I-FOBT: 79.3% p=0.15 *PPV for cancers (95% CI)* G-FOBT: 5.2% (3.0–7.3) I-FOBT: 5.9% (4.4–7.4) p=0.596 *PPV for advanced adenoma (95% CI)* G-FOBT: 17.5% (13.8–21.2) I-FOBT: 26.9% (24.1–29.8) p=0.0001	III The I-FOBT was superior to the G-FOBT for the detection of both cancers and advanced adenomas.

Quality assessment: good representativeness of population, tests were analysed in a central analysis centre.

Colonoscopy was blinded to which test(s) proved positive.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Hughes 2005	Prospective diagnostic accuracy study	1.Immunochemical FOBT (I-FOBT, Enterix) 2. Guaiac FOBT (Hemoccult II, HOS) 3. Both tests	3,861 aged 50 to 74 years from all four practices in a rural community who agreed to participate 2,419 (72.0%) received an immunochemical kit 939 (28.0%) received a guaiac kit 503 (13.0%) received both immunochemical and guaiac kits Queensland Australia	Positive rate, PPV Multivariate relationships between advanced pathology status (diagnosis of cancer or adenoma of advanced pathology) and kit type for persons completing a kit.	***Positives results*** I-FOBT: 89 (9.5%) Hemoccult II: 11 (3.9%) Overall: 100 (8.2%) ***Positive predictive values for cancer or adenoma of advanced pathology*** I-FOBT: 37.8% (95% CI 28.1-48.6) Hemoccult II: 40.0% (95% CI 16.8-68.7) ***Advanced pathology status according to different kit test*** I-FOBT (n=935) OR: 2.44 (95% CI 0.85-6.98) Hemoccult II (n=284) OR: 1.00 (ref) p=0.10	**III** Higher positivity rates for immunochemical FOBT did not translate into higher false-positive rates, and both test types resulted in a high yield of neoplasia

Quality assessment: good representativeness of average population, low participation in screening (Overall 36.3%). No information on the blinding of outcome assessment.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Rozen 2000	Prospective diagnostic accuracy study	FOBTs combination: 1.Immunochemical FOBT (FlexSure) and 2. Guaiac FOBT (Hemoccult SENSA, HOS) Ref standard colonoscopic examination every 3–5 years, and the others have a flexible sigmoidoscopy examination every 3–5 years	1410 consecutive persons attending a CRC screening/follow-up service or to symptomatic patients coming for evaluation of abdominal complaints Mean age (SD) 60.9 ± 11 years 53% were women Israel	Sensitivity, specificity, and predictive value for Neoplasia (Adenomas of All Sizes or Carcinomas)	*Sensitivity % (CI 95%)* HOS: 35 (22-47) FlexSure: 18 (8-28) Both tests: 13 (4-22) HOS vs. FS, $p<0.05$ *Specificity % (CI 95%)* HOS: 96 (95-97) FlexSure: 99 (98-100) Both tests: 100 (99-100) HOS vs. FS, $p<0.05$ *False positive % (CI 95%)* HOS: 4.2 (3.1-5.3) FlexSure: 1.0 (0.5-1.6) Both tests: 0.3 (0.01-0.6) *False negative % (CI 95%)* HOS: 66 (53-78) FlexSure: 82 (72-92) Both tests: 87 (79-96) *PPV % (CI 95%)* HOS: 25 (23-27) FlexSure: 42 (39-44) Both tests: 64 (61-66) HOS vs. FS, $p<0.05$	**III** Guaiac HOS, which does not require dietary restrictions, is significantly more sensitive for any colorectal neoplasm than the immunochemical FS; it identifies more adenomas with a specificity that is low but acceptable for population screening

Quality assessment: population is not representative of general population (consecutive persons attending a colorectal cancer screening/follow-up service or to symptomatic patients coming for evaluation of abdominal complaints).

1.3 Effectiveness of different time interval of screening programmes (GUAIAC and immunochemical FOBT)

1.3.1 Summary document

Rita Banzi

CLINICAL QUESTION 3

Which is the best time interval for offering screening by guaiac FOBT testing?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: GUAIAC test every year
C: GUAIAC test every two years
O: Colorectal cancer mortality, overall mortality after at least 5 (10) years of follow up, colorectal cancer incidence, incidence of interval cancer
S: RCTs, systematic reviews of RCTs, cohort- and case-control studies

CLINICAL QUESTION 4

Which is the best time interval for offering screening test by immunochemical FOBT?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Immunochemical FOBT every year
C: Immunochemical FOBT every two years
O: Colorectal cancer mortality, overall mortality after at least 5 (10) years of follow up, colorectal cancer incidence, incidence of interval cancer
S: RCTs, systematic reviews of RCTs, cohort- and case-control studies

SEARCH METHOD

We contacted experts in the field to retrieve papers relevant to these issues. We also performed a search on Medline using the following keywords colorectal neoplasm, anus neoplasm, colon, adenoma, intestine, occult blood, enema, guaiac, FOBT, flexsure, hemmoquant, hemeselect, hemoccult, FIT, immudia, monohaem, insure, hemodia, immocare, magstream, endoscop*, proctoscop*, colonoscop*, sigmoidoscop*, rectosigmoidoscop*, proctosigmoidoscop*, screen*, test*, population*, surveillance, early, detect*, prevent*, time-interval, annual, biennial.

Lastly, we hand-searched references quoted the Cochrane Review "Screening for colorectal cancer using the faecal occult blood test, Hemoccult". (1)

RESULTS

The search retrieved a total of 114 papers but none of theme was specifically relevant to our PICO.

GUAIAC FOBT
We were not able to retrieve specific trials investigating the best time interval for a screening programme with GUAIAC FOBT for detecting colorectal cancer and adenomas.
However, one RCT conducted in the Minnesota area on healthy volunteers aged 50 to 80 years reported data on an annual and biennial screening programme. (2) From 1976 through 1977, a total of 46 551 study subjects were recruited and randomly assigned to an annual screen, a biennial screen, or a control group. The screen consisted of six GUAIAC-impregnated faecal occult blood tests (Hemoccult) prepared in pairs from each of three consecutive faecal samples. Participants with at least one of the six tests that were positive were invited for a diagnostic examination that included colonoscopy. All participants were followed annually to ascertain incident colorectal cancers and deaths.

Results after 13-year follow-up reported a statistically significant colorectal cancer mortality reduction in the annual screening group compared to the control group (33%; RR: 0.67 (95% CI 0.50-0.87). Biennial screening resulted in only a 6% mortality reduction. Two European trials (in England and in Denmark) subsequently showed statistically significant 15% and 18% mortality reductions with biennial screening. (3,4) A second publication of the Minnesota trial provided updated results through 18 years of follow-up and reported a colorectal cancer mortality reduction in the biennial screening group consistent with the European trials (21%, (RR 0.79, 95% CI: 0.62-0.97). (5) The analysis of the cumulative mortality rate from colorectal cancer in the Minnesota trial showed early in the study that the mortality was greater in the biennial group than in the control group and the trend was reversed by the 11th year of follow-up. Authors' conclusions were that the higher colorectal cancer mortality rate in the biennial group in the early years of the study was probably due to chance.

Immunochemical FOBT
We were not able to retrieve specific trials investigating the best time interval for a screening programme using immunochemical FOBtesting to detect colorectal cancer and adenomas. A case-control study evaluating the annual screening with immunochemical FOBT in terms of prevention of colorectal advanced cancers that require surgery, showed a reduction of 28–46% among individuals having at least one screening within 2–4 years before case diagnosis. (6) This reduction was statistically significant only for those subjects screened within the three years prior to the diagnosis.

CONCLUSIONS

No direct comparisons between annual and biennial screening programmes for colorectal cancer and adenomas by GUAIAC-FOBT and immunochemical-FOBT tests were found. From the analysis of the Minnesota trial data it can be speculated that both annual testing and biennial testing for GUAIAC-FOBT are effective methods for statistically significantly reducing colorectal cancer mortality, with the benefit from annual screening appearing to be greater than for biennial screening.

No clear recommendation regarding the best time interval for offering screening by GUAIAC and immunochemical-FOBT tests can be drawn. (LEVEL OF EVIDENCE: II-IV)

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1.3.2   Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Mandel 1999	Annual and biennial Hemoccult screening groups Control group: no screening	RCT	Volunteers recruited from the American Cancer Society (and fraternal), veterans and employee groups in the Minnesota area. 46,551 subjects aged 50 to 80 years. Screening: 1975-1982, and 1986-1992	Colorectal cancer mortality reduction Number of CRC deaths Deaths from all causes Mortality reduction	18 years follow-up	***Mortality reduction (Relative risk for CRC mortality)***: Annual screening: 33% (RR 0.67, 95% CI: 0.51-0.83) Biennial screening: 21% (RR 0.79, 95% CI: 0.62-0.97) ***Number of CRC deaths (cumulative annual mortality)***: Annual screening: 121 (9.46/1000) Biennial screening: 148 (11.19/1000) Control group: 121 (14.09/1000) ***Deaths from all causes:*** Annual screening: 5236 (342/1000) Biennial screening: 5213 (340/1000) Control group: 5186 (343/1000)	**II** The results from this study are consistent with other RCTs in demonstrating a substantial, statistically significant reduction in colorectal cancer mortality from both annual and biennial screening.

Quality assessment: adequate randomisation procedure, adequate allocation concealment. Individual random allocation of volunteers (stratified by age, sex and place of residence). Blinding of the participants not applicable. Analysis by intention to screen. High rate of subjects completed the offered screening (90% al least one screening). Blinded, standardised assessment of CRC mortality.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Mandel 1993	Annual and Biennial Hemoccult screening groups Control group: no screening	RCT	Volunteers recruited from the American Cancer Society (and fraternal), veterans and employee groups in the Minnesota area. 46,551 subjects aged 50 to 80 years. Screening: 1975-1982, and 1986-1992	Colorectal cancer mortality reduction Number of CRC cases Number of CRC deaths Deaths from all causes Mortality reduction	13 years follow-up	***Mortality reduction*** (***Relative risk for CRC mortality***): Annual screening: 33%; 0.67 (95% CI 0.50-0.87); Biennial screening: 6%; 0.94 (95% CI 0.68-1.31); ***Number of CRC cases:*** Annual screening: 323 (23/1000) Biennial screening: 323 (23/1000) Control group: 356 (26/1000) ***Number of CRC deaths (cumulative annual mortality)***: Annual screening: 82 (5.88/1000) Biennial screening: 117 (8.33/1000) Control group: 121 (8.83/1000) ***Deaths from all causes:*** Annual screening: 3361 (216/1000) Biennial screening: 3396 (218/1000) Control group: 3340 (216/1000)	**II** A significant reduction in mortality from CRC has been demonstrated as a result of annual screening with faecal occult-blood tests. The reduction observed in the biennially screened group, though not statistically significant, was consistent with the finding in the annually screened group. Additional follow-up is necessary to evaluate the efficacy of screening every two years.

Quality assessment: adequate randomisation procedure, adequate allocation concealment. Individual random allocation of volunteers (stratified by age, sex and place of residence). Blinding of the participants not applicable. Analysis by intention to screen. High rate of subjects completed the offered screening (90% al least one screening). Blinded, standardised assessment of CRC mortality.

Author, publication year	Study design	Participants	Exposure	Outcome	Results	Level of evidence Conclusions
Nakajima 2003	Case-control	**Cases** were defined as the consecutive patients clinically diagnosed as having advanced colorectal cancer (A–C stages in the Dukes classification) 40 years or older at the time of diagnosis, N=423 For each case, we randomly selected three **controls** from the list of residents in the study area N=1164 Japan	Annual Screening with immunochemical FOBT	Incidence of advanced CRC	***OR for developing an advanced colorectal cancer*** Screening within 2 yrs: 0.60 (95% CI 0.29-1.23) Screening within 3 yrs: 0.54 (95% CI 0.30-0.99) Screening within 4 yrs: 0.72 (95% CI 0.44-1.17) Screening within 5 yrs: 0.96 (95% CI 0.57-1.59)	**IV** Risk of developing advanced colorectal cancer was reduced by 28–46% among individuals having at least one screening within 2–4 years before case diagnosis, with statistical significance for those screened during the past 3 years

Quality assessment: definition of cases adequate but not representative of all the colorectal cancer patients (only clinically diagnosed CRC were included); adequate comparability among cases and controls (matched by year of birth, gender and residential area within the town or village, exposure status before case diagnosis). Blinded assessment of screening history of cases and controls.

1.4 Evidence for efficacy of sigmoidoscopy and colonoscopy

1.4.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 5

Is flexible sigmoidoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Flexible sigmoidoscopy screening test
C No screening
O: Colorectal cancer incidence, colorectal cancer mortality after at least 5 (10) years of follow up
S: (Systematic reviews of) RCTs, cohort- and case-control studies

CLINICAL QUESTION 9

Is colonoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Colonoscopy screening test
C: No screening
O: Colorectal cancer incidence, colorectal cancer mortality after at least 5 (10) years of follow up
S: (Systematic reviews of) RCTs, cohort- and case-control studies

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic. We looked at the systematic review performed by Clinical Evidence. We searched on <u>Medline</u> for further systematic reviews and primary studies published after the most up to date bibliographic search of systematic reviews. We used the following search strategy:

exp "Colorectal Neoplasms" [Mesh] OR "Colonic Polyps" [Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy" [Mesh] OR colonoscopy OR sigmoidoscopy)

The search was limited to papers published in English, French and Italian between 2007 and 2008.

RESULTS

We found four systematic reviews (1-4) which considered all the primary studies known to be published by the experts and five primary studies. So we considered in detail only the primary studies cited but not fully described in the included reviews.

<u>Sigmoidoscopy</u>:

The systematic review published in Clinical Evidence (1) considered for inclusion only the RCTs. The bibliographic search has been performed until November 2006. So it reported the results of only one small RCT (Thiis-Evensen 1999) which compares flexible sigmoidoscopy followed by immediate colonoscopy and follow up colonoscopy for positives versus no screening on 799 participants with a follow up of 13 years. The study found a statistically significant reduction for CRC incidence and a non significant difference in CRC mortality. The study also found a significant increase in overall mortality in the FS screening group, but this increase could be attributed to an excess of cardiovascular mortality. The review reports that there are three large RCTs ongoing for which results on CRC mortality and incidence are not yet allowable (5-7). The authors concluded that a single flexible sigmoidoscopy followed by immediate colonoscopy and follow up colonoscopy at 2 and 6 years in those found to have polyps on FS screening seems to reduce colorectal cancer incidence.

The other two reviews (2,3) performed bibliographic search up to September 2001 and august 2002. They included the same small RCT and cited the same large ongoing trials. They considered also the results of the three case control studies of good methodological quality which compare sigmoidoscopy with no screening (Selby 1992, Newcomb 1992, Muller and Sonnenberg 1995). Al the studies adjusted for the main confounding factors (family history of CRC, FAP, polyposis, ulcerative colitis and number of periodic health examinations). All three case control studies found a significant reduction in CRC mortality and two of them also in CRC incidence. The last systematic review (4) reported a search up to November 2004. No completed RCTs were identified which evaluated the impact of FS on colorectal cancer incidence and mortality. However, three large multi-centre trials are currently underway, with two exploring one-time screening (17,18) and one exploring repeated screening.

We considered in detail a prospective cohort study cited but not described by the review (8). It included 24744 asymptomatic men aged 40-75 years at average risk of CRC. 82.4% of participants had a FS, 17.6% had a colonoscopy. The study adjusted for major confounding and prognostic factors. People who spontaneously performed a sigmoidoscopy or a colonoscopy showed in 8 years follow up a significant reduction in overall CRC incidence and in distal cancer incidence compared with people who did not have an endoscopy. There was not a difference in proximal cancer incidence and in CRC mortality. We also considered two population screening studies (9-10) The first performed in Sweden was aimed at comparing cancer incidence and mortality among participants and nonparticipants in a population-based pilot study of colorectal cancer screening with sigmoidoscopy after a 9 yr follow up (N=1,986 subjects aged 59 to 61). Nonparticipants did not differ significantly from participants with regard to overall cancer incidence (IRR, 2.2; 95% CI, 0.8-5.9). Mortality differed statistically significantly between nonparticipants and participants (Mortality from all causes MRR, 2.4; 95% CI, 1.7-3.4; neoplastic diseases (MRR, 1.9; 95% CI, 1.1-3.5). A retrospective cohort study conducted in Canada on 39,762 men and women 50–80 yr of age reported that following negative FS the incidence of distal but not proximal CRC was reduced for up to 7 yr (RR 0.69; 95% CI 0.40-0.99). Following a positive FS, the incidence of distal and proximal cancer did not differ from the Ontario population.

<u>Colonoscopy</u>

The review of Clinical Evidence underlines that there are no RCTs published or ongoing and conclude that there are no clinically important results about the effects of colonoscopy.

The other two reviews consider also the only prospective observational study on colonoscopy (Winawer 1993). This study estimated that 76% to 90% of cancer could be prevented by regular colonoscopic surveillance by comparing the CRC incidence in population which underwent colonoscopy and removal of detected polyps with three reference populations. Both reviews underline that these results should be interpreted with caution because the study used historical controls which were not

from the same underlying population. One review refers that many cross-sectional surveys have been done recently showing that colonoscopy is more sensitive than sigmoidoscopy in detecting adenomas and cancers and that this increased sensitivity could translate into increased effectiveness.

We also included a case-control (11) and a retrospective cohort study (12) which investigated CRC incidence and mortality among subjects who received colonoscopy with polypectomy compared to subjects who did not undergo colonoscopy after polypectomy. In a German study (8) 454 patients with a first diagnosis of invasive CRC aged 30 or older were matched with 391 community-based control subjects randomly selected from population registries. Compared with subjects who had never undergone large bowel endoscopy, subjects with a history of polypectomy had a strongly and significantly reduced risk of colorectal cancer for up to 5 yr, even after detection and removal of high-risk adenomas (Odds ratios (95% CI) of CRC up to 2 yr, 3–5 yr, and 6–10 yr after polypectomy were 0.16 (0.09–0.69), 0.27 (0.08–0.87), and 1.90 (0.67–5.43), respectively). A retrospective study conducted in Denmark on 2 041 patients aimed to demonstrate a possible benefit from long term (1-24 years) colonoscopic surveillance in a population of patients with all types of adenomas regardless of size and method of removal. Initial removal and subsequent colonoscopic surveillance was associated with a significant reduction of incidence (35%) of CRC as well as mortality (88%) from CRC compared to a standard population (CRC incidence RR: 0.65 (CI95% 0.43_0.95) CRC mortality RR 0.12 (CI95% 0.03_0.36)).

CONCLUSIONS

<u>Sigmoidoscopy</u>
FS seems to be a promising screening test. The only RCT is small and consequently could not have had the power to detect a statistically significant difference in CRC mortality. It is necessary to wait for the results of the three large ongoing RCTs before drawing definite conclusions about the effectiveness on CRC incidence and mortality) Cohort studies suggested that the benefit of FS could be confined to the distal colon. (LEVEL OF EVIDENCE III)

<u>Colonoscopy</u>
Very little evidence exists on the effectiveness of colonoscopy in lowering CRC incidence and mortality. From one cohort study it has been estimated that 76% to 90% of cancer could be prevented by regular colonoscopic surveillance (LEVEL OF EVIDENCE III).

The risk of CRC among patients with polypectomy appears to be reduced compared with subjects who never underwent large bowel endoscopy (LEVEL OF EVIDENCE IV)

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1.4.2 Evidence tables

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	n. of included studies	Results	Level of evidence
Clinical Evidence 2007	Flexible sigmoidoscopy Colonoscopy Control intervention: no screening	**Sigmoidoscopy** case control studies **Colonoscopy** Cohort studies with historical controls, cross-sectional studies	Asymptomatic subjects at average risk of CRC	CRC Mortality Cancer incidence	**Sigmoidoscopy** 1 small RCT (Thiis-Evensen) **Colonoscopy** No RCTs	**Sigmoidoscopy** <u>CRC mortality</u> FS does not reduce CRC mortality RCT: RR 0.50 (CI95% 0.10-2.72) <u>Cancer incidence</u> FS reduces CRC incidence RCT, follow up 13 years RR 0.2 (CI95% 0.03-0.95) **Colonoscopy** There are no clinically important results about the effects of colonoscopy	**Sigmoidoscopy** CRC mortality: moderate quality evidence CRC incidence: high quality evidence

SR FS and colonoscopy screening - Clinical Evidence 2007

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE, EMBASE, COCHRANE LIBRARY, NHS CENTRE OF REVIEW AND DISSEMINATION, TRIP, NICE.
	Date restriction	Form 1990 to November 2006
	any restriction	No Language restrictions
Selection	Inclusion and exclusion criteria	SRs and RCTs with minimum of 20 participants with a minimum of 8 years follow up. People at average risk of CRC over 45 years old
Validity assessment	Criteria and process used	Not described
Data abstraction	Process used	Not described
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	Yes

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	n. of included studies	Results	Level of evidence
Pignone 2002	Sigmoidoscopy Colonoscopy Control intervention: no screening	systematic review including RCTs, observational studies	Asymptomatic subjects at average risk of CRC	CRC Mortality Cancer incidence	**Sigmoidoscopy** 1 small RCT (Thiis-Evensen) 2 case control studies (Selby, Newcomb) **Colonoscopy** No RCTs 1 cohort study with historical control (Winawer) 1 case control study (Muller and Sonnenberg)	**Sigmoidoscopy** <u>CRC incidence</u>: RCT, follow up 13 years RR 0.2 (CI95% 0.03-0.95) <u>CRC mortality</u> Case control studies: : 59% reduction (CI95% 31%-75% RCT: RR 0.50 (CI95% 0.10-2.72) **Colonoscopy** <u>CRC incidence</u>: Cohort study: reduction of 76%-90%. Case control study: OR 0.47 (CI95% 0.37-0.58 for colon cancer; OR 0.61 (CI95% 0.48-0.77) for rectal cancer <u>CRC mortality</u>: OR 0.43 (CI95%0.30-0.63	Sigmoidoscopy **II, IV** Colonoscopy **III**

SR FS and colonoscopy screening - Pignone 2002

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE AND REFERENCES FROM RETRIEVED PUBLICATIONS.
	Date restriction	Form 1966 to September 2001
	any restriction	Language restrictions not mentioned
Selection	Inclusion and exclusion criteria	RCTs and observational studies which reported cancer mortality and incidence
Validity assessment	Criteria and process used	Not done
Data abstraction	Process used	Two reviewers examined articles for inclusion
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	Yes

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	n. of included studies	Results	Level of evidence
Walsh 2003	Flexible sigmoidoscopy Colonoscopy Control intervention: no screening	**Systematic review including :** **Sigmoidoscopy:** case control studies **Colonoscopy** Cohort studies with historical controls, cross-sectional studies	Asymptomatic subjects at average risk of CRC	CRC Mortality Cancer incidence	**Sigmoidoscopy** 1 small RCT (Thiis-Evensen) 4 case control studies (Selby, Newcomb, Muller, Kavanagh) **Colonoscopy** No RCTs 2 cohort studies (Winawer, Citarda) 2 cross-sectional studies (Imperiale, Lieberman)	**Sigmoidoscopy** <u>CRC mortality</u> Selby: OR 0.41 (CI95% 0.25-0.69) Newcomb: OR 0.21 (CI95%0.08-0.52) Muller : OR 0.41 (CI95%0.33-0.5) <u>Cancer incidence</u> Muller and Kavanagh reported reduction (data not shown) RCT demonstrated reduction (data not shown) **Colonoscopy** Cross-sectional surveys demonstrated that colonoscopy is more sensitive than FS. It can be assumed that increase sensitivity would translate into increased effectiveness. Cohort studies: Cancer incidence: reduction of 76%-90%. But authors underline that these studies were not about colonoscopy screening and used historical controls.	Sigmoidoscopy **IV** Colonoscopy **III, V**

SR FS – colonoscopy screening – Walsh 2003

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE, REFERENCE LIST OF RETRIEVED ARTICLES, EXPERT CONSULTATION
	Date restriction	Jan 1966 to august 2002
	any restriction	English Language restrictions
Selection	Inclusion and exclusion criteria	RCTs, observational studies that evaluated flexible sigmoidoscopy or colonoscopy as screening test in asymptomatic people at average risk on mortality, cancer incidence
Validity assessment	Criteria and process used	Not done
Data abstraction	Process used	Not described
Quantitative data synthesis	Measures of effect, method of combining results	Not done
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	No
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not specified
	summary results	Not for all studies

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Kavanagh 1998	Flexible sigmoidoscopy or colonoscopy Control intervention: no screening	Prospective Cohort study	24744 Asymptomatic men aged 40-75 years at average risk of CRC	CRC Mortality Cancer incidence	8 years	82.4% had a FS, 17.6% had a colonoscopy CRC incidence: RR: 0.58 (CI95% 0.36-0.96) Distal cancer incidence: RR 0.44 (CI95% 0.21-0.90) Proximal cancer incidence: RR 0.92 (CI95% 0.43-196) CRC mortality: RR: 0.56 (CI95% 0.20-1.60)	III

Quality assessment:

Representativeness of the exposed cohort: doubt about the representativeness of the cohort: extracted from health personnel: dentists, optometrists, podiatrists, osteopaths, pharmacists, veterinarians; possibly with more education and health style behaviour than general population.

Selection of the non exposed cohort: drawn from the same community as the exposed cohort.

Ascertainment of exposure: written self report.

Demonstration that outcome of interest was not present at start of study: yes.

Comparability of cohorts on the basis of the design or analysis: Most important factors of adjustment: age, dietary habits, physical activity, BMI, smoking habits, family history of CRC, intake of folate, methionine, total fat, red meat, aspirin.

Adequacy of follow up of cohorts: complete follow up - all subjects accounted for.

Author, publication year	Study design Study objective	Intervention	Participants	Outcomes	Follow up	Results	Level of evidence
Blom 2008	To compare cancer incidence and mortality among participants and nonparticipants in a population-based pilot study of colorectal cancer screening with sigmoidoscopy	Sigmoidoscopy	1,986 subjects aged 59 to 61 were invited 771 agreed to participate (39%; 385 men and 386 women) Sweden	Incidence rate ratio (IRR) of colorectal and other cancer participants vs. non participants Mortality rate ratio (MRR) Outcomes assessed by multiple record linkages to health and population registers.	Up for 9 years	***IRR of colorectal cancer*** IRR: 2.2; 95% CI, 0.8-5.9 ***IRR of other gastrointestinal cancer*** 2.7; 95% CI, 0.6 12.8 ***MRR from all causes*** 2.4; 95% CI, 1.7-3.4 ***MRR from neoplastic diseases*** 1.9; 95% CI, 1.1-3.5	**III** Nonparticipants did not differ significantly from participants with regard to overall cancer incidence. Overall, mortality differed statistically significantly between nonparticipants and participants

Quality assessment: exposed cohort was representative of the Swedish population at average risk for colorectal cancer; self-selection of the exposure status (selection bias); similar cohorts' baseline characteristics; adequate assessment of outcome (medical registers and records); adequate follow up of cohorts.

Author, publication year	Study design Study objective	Intervention	Participants	Outcomes	Follow up	Results	Level of evidence
Rabeneck 2008	population-based retrospective cohort study to estimate the annual incidence of CRC within 7 yr following FS and to identify factors associated with incident CRC in those with a negative FS.	Flexible Sigmoidoscopy (FS)	39,762 men and women 50–80 yr of age who had a negative (34,822) or positive (4,940) FS 43.1% male 1996–1998 Ontario, Canada	age- and sex-standardized incidence rates (SIR) of proximal and distal CRC Cancers/1,000 persons	up for 7 years	***SIR for distal CRC (95% CI)*** <u>Positive FS</u> 0.86 (0.10-3.17) RR vs. no FS cohort 0.80 (0.01–1.94) <u>Negative FS</u> 0.74 (0.46–1.13) RR vs. no FS cohort 0.69 (0.40–0.99) <u>No FS cohort</u> 1.07 (1.02–1.11) ***SIR for proximal CRC (95% CI)*** <u>Positive FS:</u> 2.01 (0.75-4.35); RR vs. no FS cohort 2.54 (0.52-4.57) <u>Negative FS</u>: 0.86 (0.56-1.26); RR vs. no FS cohort 1.09 (0.67-1.51) <u>No FS cohort</u>: 0.79 (0.76-0.83)	**III** SIR for distal CRC was reduced for up to 7 yr following negative FS. In contrast, the SIR for proximal colon cancer, except for year 2, did not differ between the negative FS cohort and the no FS cohort. Following a positive FS, the SIR in the seventh year of follow-up for both distal and proximal CRC did not differ from the no FS cohort. The benefit of FS was confined to the part of the rectum and colon that is examined during the procedure.

Quality assessment: exposed cohort was representative of the Ontario population; retrospective design; similar cohorts' baseline characteristics; adequate assessment of outcome (medical registers and records). Adequate follow up of cohorts.

Author, publication year	Study design Study objective	Participants	Outcomes	Follow up	Results	Level of evidence
Brenner 2007	Case control study Germany to assess the risk of CRC among patients with polypectomy (compared with subjects who never underwent large bowel endoscopy)	454 Patients with a first diagnosis of invasive CRC aged 30 or older 391 Community-based control subjects were randomly selected from population registries, employing frequency matching with respect to age, sex, and county of residence	CRC incidence among subjects who received colonoscopy with polypectomy compared to subjects who did not underwent colonoscopy	Up to 10 years	CRC incidence Polypectomy up to 10 year ago OR: 0.43 (0.25–0.74) Polypectomy up to 2 years ago 0.16 (0.06–0.43) Polypectomy up to 3-5 years ago 0.27 (0.08–0.87) Polypectomy up to 6-10 years ago 1.90 (0.67–5.43) People with advanced adenoma removed at baseline Polypectomy up to 10 year ago OR: 0.50 (0.23–1.12) Polypectomy up to 5 years ago 0.27 (0.10–0.77) Polypectomy up to 6-10 years ago 2.09 (0.41–10.69) People with no advanced adenoma removed at baseline Polypectomy up to 10 year ago OR: 0.36 (0.18–0.76) Polypectomy up to 5 years ago 0.14 (0.05–0.43) Polypectomy up to 6-10 years ago 1.76 (0.45–6.85)	**IV** Compared with subjects who had never undergone large bowel endoscopy, subjects with a history of polypectomy had a strongly and significantly reduced risk of colorectal cancer for up to 5 yr, even after detection and removal of high-risk adenomas. Although a no significantly increased risk was found between 6 and 10 yr after polypectomy, overall risk reduction within 10 yr following polypectomy remained strong and statistically significant among patients for whom no high-risk adenomas were recorded.

Quality assessment: case definition by record linkage. Community controls subjects. Most important factor for adjustment done (age, sex, and county of residence. level of school education (categories: ≤9 yr, 10–11 yr, 12+ yr), history of CRC among a first-degree relative, smoking (categories: never, ever, current), ever regular use (at least once per month for at least 1 yr) of nonsteroidal anti-inflammatory drugs (NSAIDs), any hormone therapy (HT), and body mass index (categories <20, 20–24.9, 25–29.9, 30+ kg/m2). Ascertainment of exposure by interview not blinded to case /control status. Same rate of non response rate for both groups.

Author, publication year	Study design Study objective	Participants	Outcomes	Follow up	Results	Level of evidence
Jørgensen 2007	Retrospective study Denmark To demonstrate a possible benefit from long term (1_24 years) colonoscopic surveillance in a population of patients with all types of adenomas regardless of size and way of removal	2 041 patients included from year 1978 to 2002 Were between 24 and 76 years old (average 60.8 years for men and 60.1 for women) at the initial adenoma removal. Intervals between planned colonoscopies varied between 6 and 48 months	CRC incidence CRC mortality The relative risk (RR) of CRC and death from CRC in the total study population was calculated from 1978 to 2002 by dividing the observed number by the number expected in a standard Danish population with the same age and sex distribution. The estimates of RR were adjusted for differences in the age, sex, and calendar specific rates.	Up to 24 years	CRC incidence RR: 0.65 (CI95% 0.43_0.95) CRC mortality RR 0.12 (CI95% 0.03_0.36) Overall mortality RR: 0.93 (CI95% 0.86_1.01)	**III** In a population of patients with all types of adenomas, subjected to initial removal and following colonoscopic surveillance had a significant reduction of incidence (35%) of CRC as well as mortality (88%) from CRC compared to a standard population. Long-term colonoscopic surveillance may reduce incidence of CRC as well as mortality in patients with sporadic adenomas.

Quality assessment: Population truly representative of the population with adenomas. Ascertainment of exposure by clinical records. Assessment of outcome by record linkage.

1.5 Evidence for interval of flexible sigmoidoscopy

1.5.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 6

Which is the best time interval for offering screening by flexible sigmoidoscopy?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Flexible sigmoidoscopy screening test every five year;
C: FS with other time interval
O: Colorectal cancer incidence, colorectal cancer mortality, incidence of interval cancer
S: (Systematic reviews of) RCTs, cohort- and case-control studies

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic. We also performed a MedLine search using the following search strategy: exp "Colorectal Neoplasms" [Mesh] OR "Colonic Polyps" [Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy" [Mesh] OR colonoscopy OR sigmoidoscopy) .

The search was limited to papers published in English, French, and Italian between 2007 and 2008.

RESULTS

We identified two studies which assessed the prevalence of adenomas and cancer at the second screening round by flexible sigmoidoscopy (1,2). Both are cross-sectional surveys which assess the prevalence of polyps, adenomas and cancer at the second round of screening. One study (1) repeated the sigmoidoscopy 5 years after the first screening, the other (2) 3 years later. The study of Platell found that the prevalence of adenomas or cancer was 50% less at the 2nd screening round (after 5 years); the study of Schoen found that the yield of advanced adenoma or cancer at the 2nd screening (after 3 years) was one third and one fourth, respectively, of that of first screening. Nevertheless authors of the two studies arrived at a different conclusion: Platell suggested that rescreening average risk population with flexible sigmoidoscopy at intervals longer that 5 years could be considered, whereas Schoen concluded that although the overall percentage of detected abnormalities is modest, the data raise concern about the impact of a prolonged screening interval after a negative examination.

CONCLUSIONS

Only two cross-sectional surveys have been retrieved assessing this question. Both found a significant reduction in prevalence of adenomas and cancer at the second round of screening (3 or 5 years later). Decision about the best frequency of screening rounds should consider a balance between detection rate, costs, and risk of the examination. (LEVEL OF EVIDENCE V)

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2. Schoen RE, Pinsky PF, Weissfeld JL, Bresalier RS, Church T, Prorok P & Gohagan JK (2003), Results of repeat sigmoidoscopy 3 years after a negative examination, *JAMA*, vol. 290, no. 1, pp. 41-48.

1.5.2   Evidence tables

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence
Platell 2002	2nd Flexible sigmoidoscopy five years after the first one	Cross-sectional survey	361 participants screened by FS 5 years before with no adenoma or cancers detected, without symptoms or family history aged 55-64 years at average risk of CRC. Participants invited to screening	Prevalence of cancer, adenomas	Adenomas: Initial screening: 14% 2nd screening: 8% Adenomatous polyps >5mm Initial screening: 51% 2nd screening: 32% Cancer: Initial screening :0.3% 2nd screening: 0	V

Note: only 45% of initial cohort presented for rescreening; this could be not representative of the entire cohort.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence
Schoen 2003	2nd Flexible sigmoidoscopy three years after the first one	Cross-sectional survey	9317 participants screened by FS 3 years before with no polyps or mass detected, without symptoms or family history aged 55-74 years at average risk of CRC. Participants invited to screening	Prevalence of cancer, adenomas at the 2nd screening	Presence of polyps or mass. 13.9% Adenoma or cancer: 4.1% Cancer: 0.08% Advanced adenoma: 1.2% Non advanced adenoma: 2.8% Yield of cancer at first examination: 27/10.000 Yield of cancer at the 2nd examination: 6.4/10.000 Yield of advanced distal adenomas at 1st screening: 2.5% Yield of advanced distal adenomas at the 2nd screening: 0.8%	V

Note: 80.4% of initial cohort presented for rescreening; authors tried to distinguish new lesion discovered because of improved preparation or increased dept of insertion from the really new lesion by comparing the first and second procedures for each individual with new lesion.

1.6 Evidence for efficacy of sigmoidoscopy and colonoscopy

1.6.1 Summary document

Rita Banzi

CLINICAL QUESTION 7

Which is the optimal age range during which to perform screening with FS (at younger age are lesions in the distal bowel more frequent, at older age are lesions in the proximal bowel more frequent)?

PICOS

P: General population at average risk of colorectal cancer
I: Flexible sigmoidoscopy screening
C: Not applicable
O: Colorectal cancer incidence, colorectal cancer mortality after at least 5 (10) years of follow up
S: (Systematic reviews of) RCTs, cohort- and case-control studies

CLINICAL QUESTION 11

Which is the optimal age range during which to perform screening with colonoscopy (at younger age are lesions in the distal bowel more frequent, at older age are lesions in the proximal bowel more frequent)?

PICOS

P: General population at average risk of colorectal cancer
I: Colonoscopy screening
C: Not applicable
O: Colorectal cancer incidence, colorectal cancer mortality
S: (Systematic reviews of) RCTs, cohort- and case-control studies

SEARCH METHOD

We searched on Medline using the following search strategy:
(("Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp AND "Colonoscopy"[Mesh] OR colonoscopy OR sigmoidoscopy) AND ("Age Factors"[Mesh]). The search was limited to papers published between 1999 and 2009.

We also analysed if relevant information on the optimal age range for performing screening was included in the main publications assessing flexible sigmoidoscopy and colonoscopy efficacy.

RESULTS

No relevant information on optimal age range during which to perform screening was included in the main publications assessing flexible sigmoidoscopy and colonoscopy efficacy. The majority of these studies reported screening by endoscopy in a population aged 40-75 years. (see question 5 and 9 in Chapter 1 for references).

We retrieved some evidence for this issue analysing five studies performed in the United States (1-3, 5) and in Germany(4). Three were on colonoscopy (1-3), one on flexible sigmoidoscopy (5), and one on both endoscopic techniques (4).

A cross-sectional study analysed 553 screening colonoscopies for patients aged 40 – 49 years and 352 screening colonoscopies for patients aged 50–59 years.(1) In the younger group, 79 patients (14%; 95% CI: 12%–18%) had 1 or more adenomas, of which 11 (2%; 95% CI: 1%–4% of screened) had an advanced neoplasm (>1 cm). In the 50–59 years age group, 56 patients (16%; 95% CI: 12%–20%) had 1 or more adenomas detected. Of those patients, 13 (3.7%; 95% CI: 2%–6% of screened) had an advanced neoplasm, and 1 patient (0.3%) had an adenocarcinoma detected. Although an increase in the prevalence of neoplasms in the 50–59 years age group compared with the 40–49 years age group was observed, this difference was not statistically significant.

The prevalence of neoplastic lesions in subjects aged 40–49 years was also estimated in an American cross-sectional study where 906 subjects were screened by colonoscopy(2). Among this cohort, 10.0% had hyperplastic polyps, 8.7% had tubular adenomas, and 3.5% had advanced neoplasms, none of which were cancerous. The neoplasm prevalence of the cohort older than 49 years was (0.5%; 95% CI, 0.3 to 0.9) statistically different from the younger cohort prevalence (p=0.03).

A retrospective cohort study on 404 persons aged more than 75 years who underwent colonoscopy in 1999 and 2000 at a U.S. Veterans Affairs facility investigated advanced neoplasm prevalence and the predictors of mortality of elderly persons after colonoscopy. (3) During a median follow-up of 5.95 years, 41% of the patients died, most commonly for cardiovascular causes and extracolonic malignancies. Age and declining health predicted overall mortality (Age related HR: 1.16 for each year increase beyond age 75; 95% CI, 1.07-1.3; p=0.0003; comorbidity related HR 8.3 for each point increase (Charlson score); 95% CI, 1.4-48.5; p=0.02). An advanced neoplasm at index colonoscopy and the presence of symptoms were not predictors of mortality (p=0.05).

A German case–control analysis in which the history of endoscopic screening examinations was compared between patients with a first diagnosis of colorectal cancer between ages 50 and 79 (n=386, cases) and patients with a first diagnosis of gastric cancer or breast cancer within the same age interval (n=344, controls) assessed the possible impact of various screening schemes (4). This study referred to both colonoscopy and sigmoidoscopy procedures as no definite distinction between endoscopic screening histories was made. However, considering the screening standards the majority of endoscopic examinations were likely to have been colonoscopies. For all screening schemes except those with a single endoscopy around age 50 or 70, a strong, highly significant risk reduction between 70% and 80% (as indicated by ORs between 0.30 and 0.20) was estimated. The optimal age for a single screening endoscopy appeared to be around 55 years: a single screening endoscopy at younger ages may not be sufficient to prevent occurrence of CRC at higher ages, whereas a single screening endoscopy at 60 or older would fail to prevent CRC occurrence at younger ages.

Finally, one cross-sectional study was performed on 7,388 asymptomatic subjects of which 420 subjects were ≥75 years of age (elderly) and 6968 were aged 50–74 years (general screening population) (5). Safety, tolerability, completion, and endoscopic findings were compared. The study demonstrates that elderly subjects ≥75 have an increased rate of endoscopist-reported difficulties and a higher rate of incomplete examinations compared to the general screening population, ages 50–74. Complication and detection rates of all adenomas and advanced adenomas were similar in both cohorts, while an increased detection of carcinomas in the elderly was observed.

CONCLUSIONS

No direct evidence confirming the optimal age range during which to perform screening with flexible sigmoidoscopy and colonoscopy was retrieved. From the evidence retrieved it appears that the prevalence of neoplastic lesions in the younger population (under 50 years old) is too low to justify endoscopic screening while in the elder population (≥75) tolerability could be a major issue. The optimal age for endoscopy appears to be around 55 years. (LEVEL OF EVIDENCE IV/V)

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1.6.2 Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Rundle 2008	Colonoscopic screening	Cross-sectional (screening programme)	553 screening colonoscopies for patients ages 40 – 49 (median, 45.58) years and 352 screening colonoscopies for patients ages 50 –59 (median, 53.71) years asymptomatic average-risk individuals Male in the 40 – 49 years age group: 417 (75%) Male in the 50 – 59 years age group: 271 (77%) United States	Prevalence of adenomas and cancers for those aged 40 – 49 years vs. those 50 –59 years	***40 – 49 years age group:*** <u>1 or more adenomas:</u> 79 patients (14%, 95% CI: 12%–18%) of these <u>advanced neoplasm (>1 cm):</u> 11 patients (2%, 95% CI: 1%–4% of screened) <u>Number needed to screen to find 1 advanced neoplasm:</u> 50 (95% CI: 29–100) ***50–59 years age group*** <u>1 or more adenomas:</u> 56 patients (16%, 95% CI: 12%–20%) of these <u>advanced neoplasm (>1 cm):</u> 13 (3.7% of screened 95% CI: 2%–6%) <u>number needed to screen to find 1 advanced neoplasm:</u> 27 (95% CI: 16–50) <u>adenocarcinoma:</u> 1 patient (0.3% of screened) None of the comparisons were statistically significant	**V** Although an increase in the prevalence of neoplasms in the 50–59 years age group compared with the 40–49 years age group was observed this difference was not statistically significant. Despite the similar adenoma prevalence between the 2 age groups, an increase prevalence of advanced neoplasia in the 50–59 years age group (not statistically significant, possibly because of sample size limitations) was observed

Quality assessment: data were recorded electronically in a centralized digital medical record system.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Imperiale 2002	Colonoscopy (reviewed the procedure and pathology Reports)	Cross-sectional (retrospective analysis)	3421 subjects (906 40 to 49 years of age; mean (±SD) age 44.8±7.8 61% were men; 2515 older than 49 years) September 1995 through April 2000 employer-based screening-colonoscopy program United States	Prevalence of colorectal lesions (advanced lesion was defined as an adenoma at least 1 cm in diameter, a polyp with villous histologic features or severe dysplasia, or a cancer)	<u>40 to 49 year cohort:</u> **No lesions** 78.9% **Hyperplastic polyps** 10.0% **Tubular adenomas** 8.7% **Advanced neoplasms** 3.5% none of which were cancerous **Neoplasm** <u>40 to 49 years:</u> none <u>Older than 49 years:</u> 13 cancers (9 invasive cancers and 4 carcinomas in situ) Prevalence: 0.5% (95% CI, 0.3 to 0.9). p=0.03 Cancer prevalence trend according to age: P for trend <0.001	**V** Colorectal cancer is infrequent in the 40 to 49 age group; no cancers were discovered by colonoscopy in 906 persons screened. These results are compatible with the current strategy of starting to screen for colorectal cancer at the age of 50 among persons at average risk.

Quality assessment: N/A

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Kahi 2007	Colonoscopic screening	Retrospective cohort study	404 subjects aged more than 75 years who underwent colonoscopy in 1999 and 2000 at a U.S. Veterans Affairs facility and urban county hospital mean (±SD) age 79±3 years (range, 75 to 92 years); Male: 74% (n=297) White: 70% (n=283). United States	Advanced neoplasms (colorectal cancer (CRC), polyp with high-grade dysplasia, villous histologic features, or tubular adenoma R1 cm) Survival Predictors of mortality of elderly persons after colonoscopy	5 years	***Advanced neoplasm*** 59 subjects (15%) including 8 (2%) CRC. ***Mean overall survival*** 4.1±0.1 years ***Median survival*** 5.95 years (lower 95% confidence limit 5.53 years) ***All-cause mortality predictors*** Age: hazard ratio 1.16 for each year increase beyond age 75; 95% CI, 1.07-1.3; p=0.0003) Charlson score*: hazard ratio 8.3 for each point increase; 95% CI, 1.4-48.5; p=0.02). Advanced neoplasia at index colonoscopy (including CRC): marginally associated (p=0.05)	**III** In this cohort colonoscopy was safe and yielded clinically significant findings in 15% of elderly patients. During a median follow-up of 5.95 years, 41% of the patients died, most commonly for cardiovascular causes and extracolonic malignancies. Age and declining health predicted overall mortality. An advanced neoplasm at index colonoscopy and the presence of symptoms were not predictors of mortality.

*Charlson comorbidity index is a validated scoring system used to predict mortality in longitudinal studies.

Quality assessment: retrospective design; cohort is representative of elders; 404/469 subjects underwent colonoscopy were include (reasons for exclusion fully reported); data were recorded electronically by a medical record system.

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Brenner 2005	Endoscopic screening This analysis refers to both procedures combined as no definite distinction between sigmoidoscopy and colonoscopy in the screening history was made. However, the vast majority of endoscopic examinations are likely to have been colonoscopies.	Case control (re-analysis of a large case control study to evaluate and compare the potential of a wide range of endoscopy-based screening strategies)	Cases: patients with a first diagnosis of colorectal cancer between ages 50 and 79 (n=386) Controls: patients with a first diagnosis of gastric cancer or breast cancer within the same age interval (n=344) ages of 50 and 79 in a population-based case–control study (294 cases, 254 controls) November 1996 and February 1998 Saarland, Germany	CRC risk (reduction of clinically manifest CRC)	N/A	***History of a screening endoscopy*** cases: 10.9% (32/294) controls: 27.2% (69/254) ***OR for the risk reduction associated with a previous screening endoscopy*** 0.33 (95% CI; 0.21 to 0.52) ***Risk reduction according to different screening schemes*** <u>Single screening endoscopy</u> age 50: 52% (OR: 0.48 95% CI 0.21–1.11) age 55: 73% (OR: 0.23; 95% CI 0.10–0.54) age 60: 76% (OR: 0.24; 95% CI 0.08–0.66) age 65: 72% (OR: 0.28; 95% CI 0.09–0.87) age 70: 60% (OR 0.40 95% CI 0.12–1.42) <u>Two repeated endoscopic examinations</u> ages 50 and 60: 77% (OR: 0.23 95% CI 0.10–0.56) ages 55 and 65: 79% (OR: 0.21; 95% CI 0.09–0.46) ages 60 and 70: 75% (OR: 0.25 95% CI 0.11–0.61) <u>Three repeated endoscopic examinations</u> ages 50, 60 and 70: 77% (OR: 0.23 95% CI 0.11–0.51)	IV For all screening schemes except those with a single endoscopy around age 50 or 70, a strong, highly significant risk reduction between 70% and 80% (as indicated by ORs between 0.30 and 0.20) is estimated. The optimal age for a single screening endoscopy appears to be around 55 years. A single screening endoscopy at younger ages may not be sufficient to prevent occurrence of CRC at higher ages, whereas a single screening endoscopy at 60 or older would fail to prevent CRC occurrence at younger ages.

Quality assessment: Cases and controls were compared with respect to previous endoscopic screening examinations of the large bowel; matching for both age and gender; cases and controls were recruited and interviewed in the same setting (control for the potential bias from differential recall); history of screening endoscopy was based on self-reports and could not be validated by medical records.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Pabby 2005	Flexible sigmoidoscopy (FS)	Cross-sectional	7388 asymptomatic subjects (elderly: 420 subjects ≥75 years of age; general screening population: 6968 ages 50–74 years) Mean age (±SD) elderly: 78.0 ± 2.8 General population: 58.2 ± 6.6 Similar percentage of females (55.2% vs. 52.8%; p = 0.352) Outpatient CRC screening program of Harvard Vanguard Medical Associates over the 4-year period from 1996 to 2000 Boston USA	Safety, tolerability, completion, and endoscopic findings	***Incomplete examination*** Elderly: 15.6% General population: 5.4% p = 0.0001 ***Endoscopist reported procedural difficulties*** Elderly: 50.4% General population: 34.9%; p = 0.0001 ***Complication rate*** Elderly: 1.0% General population: 1.5%; p = 0.53 ***Adenoma detection rate*** Elderly: 7.2% General population: 5.6%; p= 0.213 ***Advanced adenoma detection rate*** Elderly: 0.71% General population: 0.65%; p= 0.86 ***Carcinoma rate*** Elderly: 0.53% General population: 0.06% p= 0.042	**V** The study demonstrates that elderly subjects ≥75 years of age have an increased rate of endoscopist-reported difficulties and a higher rate of incomplete examinations compared to the general screening population, ages 50–74. Complication and detection rate of all adenomas and advanced adenomas was similar rate was similar in both cohorts, while an increased detection of carcinomas in the elderly was observed.

Quality assessment: N/A

1.7 Efficacy of combined test (FOBT + sigmoidoscopy)

1.7.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 8

Are combined tests (FOBT and flexible sigmoidoscopy) more effective than single tests (only FOBT or only flexible sigmoidoscopy)?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Combined tests (FOBT and flexible sigmoidoscopy)
C: Only FOBT or only flexible sigmoidoscopy
O: Colorectal cancer incidence, colorectal cancer mortality after at least 5 (10) years of follow up
S: (Systematic reviews of) RCTs, cohort- and case-control studies

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic. We searched on <u>Medline</u> for further systematic reviews and primary studies published after the most up to date bibliographic search of systematic reviews. We used the following search strategy:
exp "Colorectal Neoplasms" [Mesh] OR "Colonic Polyps" [Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy" [Mesh] OR colonoscopy OR sigmoidoscopy)

The search was limited to papers published in English, French, and Italian between 2007 and 2008.

RESULTS

5 studies were found addressing the question of the effectiveness of combinations of tests compared to single tests. 1 study compared the diagnostic accuracy of FOBT alone (guaiac test, Hemoccult II), FOBT+FS, FS alone (1). 3 studies (2,3,5) compared the compliance and the detection rate of FOBT alone with FOBT+FS, 2 studies (4,5) compared compliance and the detection rate of FOBT+FS compared to FS only. All but one study (4) used the guaiac test, Hemoccult II, for FOBT. In the NORCCAP trial the immunochemical FlexSure test was used. No studies were retrieved assessing the impact of different screening strategies on cancer incidence or CRC mortality.

The accuracy study (1) found that the sensitivity of FS, alone or combined with FOBT was significantly higher that the sensitivity of FOBT; the higher sensitivity was achieved by the combination of tests (FOBT alone: 23.9%, FS alone: 70.3%, FOBT+FS: 75.8%). Among all patients with proximal advanced neoplasia, combined testing would identify 50.7 % of patents.

One-time combined testing would fail to identify 24 % of patients with advanced neoplasia.

The SCORE 2 trials (5) randomised participants to receive FOBT only, FS only or a combination of FS and FOBT but the results could be used only for compliance, because the other outcomes are not presented separately for the two arms FS alone and FS +FOBT.

The trial by Rasmussen 1999 (1) randomised participants to receive FOBT only or FOBT + FS. The study by Rasmussen 2003 (2) is an indirect comparison of the results of the FOBT arm of the Funen trial (Jørgensen 2002) after 8 screening rounds and of the FOBT+FS arm of the Rasmussen 1999 trial. Finally the NORCCAP study (4) randomised participants to receive FS only or FS+FOBT. In the study by Rasmussen 2003 (3) the detection rate for cancer became similar among two strategies after 5 rounds of biennial screening. With FS+FOBT more adenoma was found if the detection rate was computed using as denominator of participants who actually were screened, but if invited persons were used as a denominator more advanced adenoma were discovered by biennial screening. However these conclusions should be considered cautiously because they come from an indirect comparison between two trials.

	FOBT	FOBT+FS	FS
compliance	55.7% (2) 65% (3), 29.1% (5)	40% (2,3), 63% (4), 28.1% (5)	67% (4), 28.1% (5)
Detection rate for cancer	0.07% (2), 9.9 ‰ (3)	0.2% (4), 0.2 (2), 6.6‰ (3)	0.2% (4)
Detection rate for high risk /advanced adenoma	6.5 ‰ (3)	2.6% (4), 2.7 ‰ (3)	2.8% (4)
PPV cancer	5.5% (2)	FOBT+FS+: 9% (4), 27% (2) FOBT+FS-: 2% (4), 0 (2) FOBT-FS+:0.5% (4), 1% (2)	
PPV advanced/high risk adenoma />10mm	19% (2)	FOBT+FS+:55% (4), 42% (2) FOBT+FS-:3.8% (4), 4% (2) FOBT-FS+:20.7% (4), 14% (2)	

CONCLUSIONS

No studies have been retrieved assessing the impact of combined modality on cancer incidence or mortality. The accuracy and the detection rate are higher for FS+FOBT than FOBT alone if only one round of all screening modalities is considered. The addition of FOBT to FS does not improve significantly the detection rate on any neoplasia or cancer. Compliance is significantly higher for FOBT alone than for FS alone or FS+FOBT combined, so the balance between higher detection rate but lower compliance of FS (alone or combined) should be considered. If many rounds of biennial screening with FOBT alone are compared with once only FOBT+FS, the difference in the detection rate disappears. Moreover using the detection rate among those invited to screening and not among those who were actually screened, resulted in more CRC being detected in the biennial FOBT program because of the higher compliance of the FOBT alone programs (LEVEL OF EVIDENCE I).

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1.7.2   Evidence tables

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Lieberman 2001	Flexible sigmoidoscopy + FOBT guaiac (Hemoccult II) Reference standard : colonoscopy Sigmoidoscopy was defined as examination of the rectum and sigmoid colon during colonoscopy	Cross-sectional diagnostic accuracy study USA	2,885 Asymptomatic subjects (age range, 50 to 75 years)	Sensitivity Specificity For Advanced colonic neoplasia defined as an adenoma 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer.	Sensitivity FOBT alone: 23.9% Sigmoidoscopy alone: 70.3% FOBT+ sigmoidoscopy, FOBT first: 75.8% FOBT+ sigmoidoscopy, sigmoidoscopy first : 75.8% Specificity FOBT: 93.8%	**III** Combined screening with a FOBT and sigmoidoscopy would identify 75.8 percent of subjects with advanced neoplasia (95 %CI, 71.0 to 80.6), a small and statistically non significant increase in the rate of detection as compared with sigmoidoscopy alone. Among all patients with proximal advanced neoplasia, combined testing would identify 50.7 % of patents. One-time combined testing would fail to identify 24 % of patients with advanced neoplasia

Quality assessment:

Spectrum of patients is representative of patients who will receive the test in practice.

Selection criteria clearly described.

The whole sample received the reference standard (avoidance of verification bias) .

Execution of the index test and reference standard clearly described.

Withdrawals from the study explained.

Author, publication year	Screening test evaluated Control intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Rasmussen 1999	Exp: Flexible sigmoidoscopy + FOBT guaiac (Hemoccult II): 5495 Control : FOBT alone:5493 Subjects positive underwent colonoscopy	RCT Denmark	10,978 Asymptomatic subjects (age range, 50 to 75 years)	Compliance Detection rate Positive predictive value Cancer incidence during follow up	24-62 months	Compliance: FOBT: 55.7% FOBT+FS: 40.4% (P<0.0001) Detection rate for cancer FOBT: 4/ 5493 FOBT+FS: 12/5495 PPV carcinoma FOBT alone: 5.5% FOBT+FS+: 27% FOBT-FS+:1% FOBT+FS-: 0 PPV adenoma ≥10 mm FOBT alone: 19% FOBT+FS+: 42% FOBT-FS+:14% FOBT+FS-: 4% Cancer incidence during follow up: FOBT: 18/3055:0.6% FOBT+FS: 8/2222: 0.36%	II Despite lower compliance FS+FOBT had a higher detection rate of cancer and adenomas. FOBT did not add anything to the predictive value of FS in the present studies, but the total number of screen detected cancers was small to draw definite conclusions. The rather advanced interval cancer occurring within a short time, in spite of being less frequent after screening with FS+FOBT rather than with FOBT alone, suggest that once only FS may not be an optimal screening strategy

Quality assessment:
Allocation concealment: adequate: central randomisation procedure on the basis of general population register, adjusting for married couples, who were allocated to the same group; double blinding: not possible; lost at follow up: only five people positive refused further examination; 12 people in the FOBT alone group and 6 in the FOBT+FS lost at follow up because of migration.

Author, publication year	Screening test evaluated Control intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Rasmussen 2003	Exp: Flexible sigmoidoscopy + FOBT guaiac (Hemoccult II): 5495 Control : FOBT alone, biennial :24963 Subjects positive underwent colonoscopy	Results of the experimental arm of the Funen trial (Jørgensen 2002) (FOBT Hemoccult II, 8 screening round) and of the experimental trial of Rasmussen 1999 (FOBT+FS) compared Denmark	30,458 Asymptomatic subjects (age range, 50 to 75 years)	Compliance Detection rate	24-62 months for the FOBT+FS 16 years for the biennial FOBT	Compliance: FOBT: 65% in the first screening round FOBT+FS: 40.4% Detection rate cancer in screened persons FOBT: 9.9/1000 after 8 round FOBT+FS: 6.6/1000 The yield became similar after 5 screening round Detection rate advanced adenoma FOBT: 23/1000 after 8 round FOBT+FS: 33/1000 Detection rate in invited persons FOBT: 6.5/1000 after 8 round FOBT+FS: 2.7/1000	**II** Indirect comparison of the results of two trials started 7 year apart and on the same population. No significant difference was demonstrated in detection rates of CRC in the two screening strategies, but more advanced adenomas were found by FS+FOBT. Using the detection rate among those invited to screening and not among those who were actually been screened, resulted in more CRC being detected in the biennial FOBT program. In other words, once only FS+FOBT cannot compete with biennial FOBT unless compliance is much higher than the 40% reported

Quality assessment: indirect comparison of two trials performed on the same population started 7 years apart and with different follow–up.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
NORCCAP study 2003	1.one only FS (n.10013) 2. once only FS + FOBT Immunochemical -FlexSure (n.9990) Norway	RCT	20,780 Random sample of general population aged 55-64 years n. 20003 Norway	Compliance Detection rate for cancer or adenoma PPV	<u>Compliance</u>: FS +FOBT arm: 63% FS only arm: 67% <u>PPV for cancer</u>: both FOBT and FS positives: 9% FS negative, FOBT positive: 2% FS positive, FOBT negative: 0.5% <u>PPV for high risk adenoma</u>: both FOBT and FS positives: 55.4% FS negative, FOBT positive: 3.8% FS positive, FOBT negative: 20.7% <u>Detection rate for any neoplasia</u> (intention to diagnose) FS +FOBT arm: 11% FS only arm: 12% Cancer: FS +FOBT arm: 0.2% FS only arm: 0.2% High risk adenoma: FS +FOBT arm: 2.6% FS only arm: 2.8% Low risk adenoma: FS +FOBT arm: 8.0% FS only arm: 8.7%	**II** In the present study the addition of FOBT does not contributed substantially in the improvement of detection rate

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome and the other outcomes are related to test performance; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is not feasible for the kind of intervention compared.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2005 (SCORE 2)	1.biennial immunologic FOBT delivered by mail 2. biennial immunologic FOBT delivered by GP 3 once only sigmoidoscopy 4. FS followed by biennial FOBT 5 patient choice between once only FS and FOBT	Multicentre RCT	Random sample of general population aged 55-64 years n. 26682 Italy	Positive results: polyp or mass Inadequate test Incomplete test Compliance % with further investigation % cancer or adenoma Adverse effect of colonoscopy) Complication of sigmoidoscopy Adverse events of FOBT (FP rate, FN rate)	Compliance: FOBT (1+2): 29.1% FS only: 28.1% FS+ FOBT: 28.1% positive rates: FOBT (1+2+5): 4.3% FS (3+4+5): 18.6% further investigation FOBT (1+2+5): 4.3%; 87.7% of positives accepted FS (3+4+5):7.6% of the all sample cancer or adenomas: FOBT (1+2): 1.8% cancer detection 3.4/1000 FS (3+4+5): 5.1% cancer detection rate:3.5/1000 positive predictive value: FOBT:45.8% of the colonoscopy performed; 40% of the positives FS: 6. 7% inadequate test FS(3+4+5): 8.1% (FS) incomplete test FOBT (1+2+5):23.3% (colonoscopy) FS(3+4+5):12.9%(FS) FS(3+4+5)::13% (colonoscopy) adverse effects of colonoscopy: 0.3% Minor self limited complication: 3.9% complication of sigmoidoscopy: 1case of severe vagal reaction and apparent cardiac arrest. Minor self limited complication: 0.5%	II Participation to a mass screening in Italy would not be different if FOBT or FS had offered. The detection rate of advanced neoplasia was statistically significantly higher for FS than for FOBT. A limitation of the study is that it compares only one round of FOBT vs. FS.

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome and the other outcomes are related to test performance; detection bias: blinding of outcome assessor: not relevant because the outcome measures are objectives and because it is not feasible for the kind of intervention compared.

1.8 Best time interval for offering screening test by colonoscopy

1.8.1 Summary document

Rita Banzi

CLINICAL QUESTION 10

Which is the best time interval for offering screening by colonoscopy?

PICOS:

P: General population at average risk of colorectal cancer aged 50 years and older
I: Colonoscopy screening test every ten year
C: Colonoscopy with other time interval
O: Colorectal cancer incidence, colorectal cancer mortality
S: (Systematic reviews of) RCTs, cohort- and case-control studies
PRIORITY: High

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic.
We also performed a MedLine and Embase search from 1966 to 2008 using the following search strategies:
(((("Mass Screening/methods"[Mesh] OR "Mass Screening/organisation and administration"[Mesh])
OR ("Colonoscopy"[Mesh])) AND ("Colorectal Neoplasms/diagnosis"[Mesh] OR "Colorectal
Neoplasms/epidemiology"[Mesh] OR "Colorectal Neoplasms/pathology"[Mesh] OR "Colorectal
Neoplasms/prevention and control"[Mesh]) OR "Adenomatous Polyps"[Mesh] OR Adenoma) AND
("Time Factors"[Mesh]) AND ((Humans[Mesh]) AND (English[lang]))) AND "interval" AND
((Humans[Mesh]) AND (English[lang]));
("Follow-Up Studies"[Mesh]) AND (("Colonoscopy"[Mesh]) AND ("Colorectal
Neoplasms/epidemiology"[Mesh])).

RESULTS

Following the screening of titles and abstracts nine observational studies were considered relevant for this issue. (1-9). One has a case control design (1), four are prospective (5, 6, 8, 9) and four are retrospective cohort studies (2-4, 7).

A German case-control study investigated patients with a first diagnosis of primary invasive colorectal cancer detected because of symptoms or incidentally (rather than by screening) and aged 30 or older (N = 380) (1). After adjustment for the matching factors age and sex and other potential confounding variables, a previous negative colonoscopy was associated with a 74% lower risk of CRC (adjusted odds ratio adjOR=0.26 (95% CI, 0.16 to 0.40)). This risk reduction persisted throughout 20 years as demonstrated by the stratification of results with respect to the time interval of the last negative

colonoscopy (1-2 years adjOR = 0.16 (95% CI 0.07-0.36); 3-4 years adjOR = 0.29 (95% CI 0.13-0.68); 5–9 years adjOR = 0.25 (95% CI 0.09-0.69); 10–19 years adjOR = 0.33 (95% CI 0.12-0.91); 20+ years adjOR = 0.46 (95% CI 0.16-1.32)).

Similar results were obtained in a population-based cohort retrospective analysis conducted on 35,975 citizens of the Canadian Manitoba province (7). The estimation of CRC incidence in a population with negative colonoscopy was obtained by matching data from the Manitoba health population registry and the Cancer registry. The incidence of CRC was 1.1 cancers per 1000 person-years of follow-up. Compared with the expected incidence in the same population, this was 31% lower than expected and remained reduced beyond 10 years after the negative colonoscopy. In particular, the standardised incidence ratio (SIR) for individuals who did not have repeat endoscopy for 2, 5, or 10 years after an initial negative colonoscopy were 0.54 (95% CI 0.44-0.66), 0.50 (95% CI 0.34-0.71), 0.20 (95% CI 0.02-0.72), respectively.

A prospective cohort study conducted on 4,084 subjects involved in a Japanese annual screening programme which had a negative colonoscopy reported an incidence of 20.8% for any type of neoplasia and 0.73% for advanced adenoma respectively (3 year follow up)(9). Data on a cohort of 1047 patients with normal baseline colonoscopy extracted from a multicenter endoscopic databases reported an incidence of 0.5% (2).

A retrospective cohort study investigated the incidence of adenoma at follow up examinations (4.3 years) according to the baseline findings. Incidence of adenoma in the hyperplastic polyps group at the baseline was higher than that reported for the negative colonoscopy group (18/41, 43% vs. 77/362, 21%, respectively) (4).

Smaller studies were also retrieved. One study selected 29 patients with colorectal cancer who had one or more negative colonoscopies before the diagnosis and assessed the stage of cancer and the interval between diagnosis and the previous examination(3). Authors concluded that size, differentiation and stage of colorectal cancer, in addition to the interval to diagnosis, suggest that the majority of cancers followed prior false negative examinations. A similar cohort study enrolling 29 patients aged 50-70 years who had no prior history of polyps and had a normal colonoscopy at least 5 yr earlier showed that the incidence of adenomatous polyps after a mean of 5.74 yr was 41.4% (95% confidence interval: 23.5-61.1%)(8).

The incidence of adenoma was also assessed within a surveillance study in a sub-cohort of 298 male patients aged 50-70 years with no neoplasia at baseline screening colonoscopy(5). A follow up colonoscopy performed within 5.5 years from the baseline showed a 24.8% rate of any adenoma while the rate of advanced adenoma was 2.4%, including 1 (0.3%) cancer. As a strong association between results of baseline screening colonoscopy and rate of serious incident lesions during 5.5 years of surveillance was observed, the quality in the performance of colonoscopy appeared crucial. Similar incidence was reported in a cohort study conducted by Rex et al.on 158 (68% males) subjects with a mean age of 65.6 (55-82) years: a 27% incidence of adenomas after a negative colonoscopy in an average-risk population with a follow up of 5.5 years was observed. (6) Regular use of NSAIDs predicted a lower incidence of adenoma (OR: 0.42; 95% CI 0.18-0.96).

CONCLUSION

Adenoma incidence ranging from 24.8-41.4% was observed in an average risk population 5 years after a negative colonoscopy; this incidence can be considered similar to that of average-risk individuals. Two large observational studies suggest that screening colonoscopies do not need to be performed at intervals shorter than 10 years after a negative examination. This time interval could be extended to 20 years. (LEVEL OF EVIDENCE III/IV)

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1.8.2   Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Brenner 2006	Cases: patients with a first diagnosis of primary invasive colorectal cancer detected because of symptoms or incidentally (rather than by screening) were included

Controls: community based control subjects | Population based case-control study | Cases = 380
Controls = 485
30 years old or older

Germany | To assess the long term risk of clinically manifest colorectal cancer among subjects with negative findings at colonoscopy | Negative colonoscopy Any time ago
Cases: 30 (7.9%)
Control: 134 (27.6%)
Adj OR = 0.26 (95% CI 0.16-0.40)
Negative colonoscopy 1–2 years ago
Cases: 7 (1.8%)
Control: 50 (10.3%)
Adj OR = 0.16 (95% CI 0.07-0.36)
Negative colonoscopy 3–4 years ago
Cases: 8 (2.1%)
Control: 31 (6.4%)
Adj OR = 0.29 (95% CI 0.13-0.68)
Negative colonoscopy 5–9 years ago
Cases: 5 (1.3%)
Control: 23 (4.7%)
Adj OR = 0.25 (95% CI 0.09-0.69)
Negative colonoscopy 10–19 years ago
Cases: 5 (1.3%)
Control: 17 (3.5%)
Adj OR = 0.33 (95% CI 0.12-0.91)
Negative colonoscopy 20+ years ago
Cases: 5 (1.3%)
Control: 13 (2.7%)
Adj OR = 0.46 (95% CI 0.16-1.32) | IV

Subjects with previous negative colonoscopy had a 74% lower risk of colorectal cancer than those without previous colonoscopy.
This low risk was seen even if the colonoscopy had been done up to 20 or more years previously.
Time interval could be extended to 20 years, or if repeat colonoscopies might not be needed at all |

Quality assessment: community based control subjects matched with respect to age, sex, and county of residence; data collected through standardised personal interviews (trained interviewers); when possible, information on diagnostic process was confirmed by pertinent medical records comparability. Odds ratio were adjusted for age, sex, education, participation to general health screening examination, family history of CRC, smoking body mass index, ever regular use of NSAIDs and HRT.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Ee 2001	Retrospective cohort study Australia	1047 patients with normal baseline colonoscopy Data extracted from a multicenter endoscopic databases	Cancer incidence	5 years	Cancer incidence: 5/1047 (0.5%)	III

Quality assessment:

Population truly representative of the population at average risk.

Ascertainment of exposure by clinical records.

Assessment of outcome by record linkage.

No subjects lost to follow.

Author, publication year	Study design	Participants	Outcomes	Results	Level of evidence
Gorski 1999	Retrospective study USA	29 patients operated for rectal cancer who had one or more negative colonoscopy before diagnosis	Stage of cancer. Interval between prior colonoscopy and diagnosis	Stage of cancer: Stage 0:7 Stage I: 10 Stage II: 8 Stage II: 4 Mean interval since prior colonoscopy in patients with poorly differentiated cancer: 26 months Mean interval since prior colonoscopy in patients with well or moderately differentiated cancer: 22 months	IV Size, differentiation and stage of colorectal cancer in addition to the interval to diagnosis suggest that the majority of cancers followed prior false negative examinations.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Huang 2001	Retrospective cohort study USA	404 patients with baseline colonoscopy (362 without neoplasia and 41 with hyperplastic polyps at baseline colonoscopy)	Incidence of adenoma at follow up examinations basing on baseline findings	4.3 years	Incidence of adenoma Hyperplastic polyps at baseline: 18/41 (43%) Negative colonoscopy at baseline: 77/362 (21%)	**III** Patients found to have hyperplastic polyps at baseline may have twice the risk of adenomas on follow up as compared with those who have clean initial examinations.

Quality assessment:

Population truly representative of the population at average risk.

Ascertainment of exposure by clinical records.

Assessment of outcome by record linkage.

No subjects lost to follow.

Author, publication year	Intervention	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Lieberman 2007	Surveillance in patients following colonoscopy	Prospective Cohort study	3121 asymptomatic patients aged 50-70 years enrolled in 13 Veterans Affairs Medical Centres USA	5.5 years	Incidence rate of advanced neoplasia in patients with and without neoplasia at the baseline screening colonoscopy Association between baseline endoscopic findings and subsequent risk of advanced neoplasia	***Patients without neoplasia at the baseline*** 1950 ***At least 1 follow-up colonoscopy within 5.5 years*** 298/501 (59.5%) ***No advanced neoplasia*** 291/298 (97.6%) ***Incidence of any adenoma*** 74/298 (24.8%) ***Incidence of advanced neoplasia*** 7/298 (2.4%) ***HGD/cancer per 1000 person-yr*** 0.7 (95% CI 0–2.0) ***Advanced Neoplasia at Follow-up Colonoscopy*** <u><3 yrs[a]</u>: 0/17 (0%) <u>3-5.5 yrs[b]</u>: 6/281 (2.1%) <u>Repeat surveillance[c]</u>: 1/7 (14.3%) <u>Cumulative[d]</u>: 7/298 (2.4%) ***Relative risk in patients with baseline neoplasia*** <u>Patients with 1 or 2 tubular adenomas <10 mm</u>: 1.92 (95% CI: 0.83–4.42); <u>Patients with 3 or more tubular adenomas <10 mm:</u> 5.01 (95% CI: 2.10 –11.96); <u>Patients with tubular adenoma >10 mm:</u> 6.40 (95% CI: 2.74 – 14.94); <u>Patients with villous adenoma:</u> 6.05 (95% CI: 2.48 –14.71); <u>Patients with adenoma with high-grade dysplasia:</u> 6.87 (95% CI: 2.61–18.07)	**III** A strong association between results of baseline screening colonoscopy and rate of serious incident lesions during 5.5 years of surveillance was observed.

[a]Results of patients who had their first follow-up colonoscopy <3 years after completion of the baseline colonoscopy.

[b]Results of patients who had their first follow-up colonoscopy during years 3–5.5 after completion of the baseline colonoscopy.

[c]These results summarize the endoscopic results in patients who had a second or more surveillance examination(s).

[d]Cumulative result represents the most advanced lesion found on any colonoscopy during 5.5 years of follow-up.

Quality assessment: the selected population is representative of men. Adequate ascertainment of exposure. All pathology was reviewed locally and sent for blinded central pathology review. High rate of patients lost at follow up (reasons clearly reported). Adequate follow up.

Author, publication year	Intervention	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Rex 1996	Second colonoscopy after a negative one	Prospective cohort study	158 (68% males) subjects 154 complete cecum colonoscopy Mean age: 65.6 (55-82) years USA	5.5 years	Incidence of adenomas after a negative colonoscopy	***Incidence of adenoma*** 27% ***Incidence of advanced adenoma*** 0% ***Predictive factors*** <u>Age</u> >65: 24/75 (33%) 60-65: 11/49 (22%) 55-59: 6/30 (20%) p=0.22 <u>Hyperplastic polyps at 1st examination</u> Present: 6/27 (22%) Absent: 35/127 (28%) p=0.66 <u>NSAID use</u> Regular: 10/56 (18%) Not regular: 31/98 (32%) p=0.04; OR=0.42 (95% CI 0.18-0.96) <u>Sex</u> Men: 32/104 (31%) Women: 9/50 (18%) p=0.13	**III** In average-risk population the interval between screening examinations can be safely expand beyond 5 years, provided the initial provided the initial examination is a carefully performed complete colonoscopy that is negative for colonic adenomas or cancer.

Quality assessment: the population was a subset of colonoscopy screening population; the screening programme was stopped before the remaining eligible persons were invited. Reasons for screening refusal clearly reported. Factor analysed in the multivariate logistic regression: age, sex, presence of hyperplastic polyp(s) at the initial examination, and regular NSAID use. Review of the pathological slides of incident polyps was performed by the study pathologist. Adequate follow up.

Author, publication year	Intervention	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Singh 2006	All individuals who had undergone colonoscopy or sigmoidoscopy in Manitoba between April, 1984 and December 2003 and had negative results	Population-based cohort retrospective analysis	N = 35975 (colonoscopy cohort) Canada	Up to 10 years	Incidence of colorectal cancer measured by SIR	SIR 0.69 (95% CI, 0.59-0.81) at 6 months, 0.66 (95% CI, 0.56-0.78) at 1 year, 0.59 (95% CI, 0.48-0.72) at 2 years, 0.55 (95% CI, 0.41-0.73) at 5 years, and 0.28 (95% CI, 0.09-0.65) at 10 years.	**III** Screening colonoscopies do not need to be performed at intervals shorter than 10 years.

Quality assessment: good representativeness and reliability of the exposures of the cohort as the population selection was obtained matching two registers (the Manitoba Cancer registry and the Manitoba health population registry) - avoidance of recall bias. Colorectal cancer incidence in the cohort was compared with the age-, sex-, and calendar-year−adjusted CRC incidence rates in Manitoba and expressed as standardized incidence ratios (SIRs). Adequate follow up.

Author, publication year	Intervention	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Squillace 1994	Follow up colonoscopy after a normal colonoscopy	Prospective Cohort study	29 (96.6% males) with no prior history of polyps Aged 50-70 years USA	5.7 years	Incidence of adenomatous polyps	***Incidence of adenoma*** 41.4% (95% CI 23.5-61.1) ***Incidence of advanced adenoma*** 3.4%	**III** The incidence of adenomatous polyps 5 years after a normal colonoscopy was similar to that of average-risk individuals.

Quality assessment: the selected population is representative of men; random selection of subjects; centralised examination of colonoscopies; adequate follow up.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Yamaji 2004	Prospective cohort study Japan	6,225 asymptomatic subjects participating in an annual colonoscopic screening program and completing three or more colonoscopies	Incidence of neoplasia at follow up examinations basing on baseline findings. Recurrence of any neoplasia	3 years	Subjects with no neoplasms at the initials two colonoscopies: 4084 Incidence of any type of neoplasia: 848/4084 (20.8%) Estimated annual incidence rate: 7.2% Incidence of advanced adenoma: 30/4084 (0.73%) Estimated annual incidence rate: 0.21% Estimated annual incidence rate stratified for sex and age of any neoplasia: Female <40 : 3.1% (CI95% 1.3-6.3) Female 40-49: 3.2% (CI95%2.4-4.2) Female 50-59: 6.7% (CI95% 5.4-8.4) Female>60: 7.3% (CI95%4.5-11.3) Male <40: 4.7% (CI95%3.9-5.9) Male 40-49: 8.2% (CI95%7.5-9.2) Male 50-59: 10.1% (CI95%9.0-11.7) Male>60: 11.4% (CI95%9.1-14.2) Subjects with adenoma removed at baseline. 2141 Recurrence of any neoplasia: 659/2141 (30.8%)	III The incidence rate in subjects with no neoplastic lesions is quite high.

Quality assessment:

Population truly representative of the population at average risk.

Ascertainment of exposure by clinical records.

Assessment of outcome by record linkage.

Only 6225 out of 68053 who were first screened had at least three colonoscopies.

1.9 Efficacy and diagnostic accuracy of CT colonography

1.9.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 12

Is CT colonography screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?

PICOS:

P: General population at average risk of colorectal cancer aged 50 years and older
I: CT colonography screening test
C: No screening
O: Colorectal cancer incidence, colorectal cancer mortality
S: (Systematic reviews of) RCTs, cohort- and case-control studies

CLINICAL QUESTION 12 B

Is CT colonography comparable to colonoscopy in test performance characteristics (sensitivity and specificity)?
P: Asymptomatic population
I: CT colonography
C: Colonoscopy
O: 1. Sensitivity / detection rate. 2. Specificity
S: (Systematic reviews of) diagnostic accuracy studies

SEARCH METHOD

We first searched systematic reviews assessing the effectiveness of CT colonography in reducing colorectal cancer incidence or mortality and assessing the diagnostic accuracy of CT colonography. Then we searched primary studies and we considered for inclusion only the prospective studies published after the more up to date bibliographic search of systematic reviews; we therefore included studies published since 2006, but not the three studies published in 2007 already included in the review of Whitlock 2008 (Johnson 2008, Kim 2007, and Johnson 2007).

Database searched: <u>Medline</u>, <u>Embase</u>, and <u>Cochrane Library</u>

<u>Search strategy for studies on prognosis</u>:
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR

colorectal neoplasm* OR colonic polyp*) AND ("Colonoscopy"[Mesh] OR colonoscopy) AND ("Colonography, Computed Tomographic"[Mesh] OR colonography)
in Title, Abstract or Keywords

Search strategy for systematic review on diagnostic accuracy
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND ("Colonoscopy"[Mesh] OR colonoscopy) AND ("Colonography, Computed Tomographic"[Mesh] OR colonography)
AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*) AND systematic [sb]
Limits: Publication Date from 2000, Humans, English, French, Italian, Spanish

Search strategy for primary studies on diagnostic accuracy
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND ("Colonoscopy"[Mesh] OR colonoscopy) AND ("Colonography, Computed Tomographic"[Mesh] OR colonography)
AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*)
Limits: Publication Date from 2000, Humans, English, French, Italian, Spanish

RESULTS

We didn't find any systematic review or primary study assessing the effectiveness of CT colonography in reducing colorectal cancer incidence or mortality.

We retrieved seven systematic reviews published since 2003 and 2008 (1-7). All assessed the diagnostic accuracy of CT colonography using colonoscopy as reference standard. The results are summarized in the table below. All results are expressed as per patient sensitivity and specificity.

We also retrieved 11 primary prospective studies published after the more recent bibliographic search of systematic reviews. Six studies were excluded. One (9) because it didn't report the data necessary to compute the sensitivity and specificity. Another study was excluded because it computed sensitivity any specificity for any colonic lesion, including non neoplastic disease (11). A third study was excluded because of the retrospective design and because it reported per polyp and not per patient sensitivity and specificity (13). Two studies were excluded because they reported only the per polyp sensitivity and specificity (14,18). A further study was excluded because it was not a diagnostic accuracy study using the index test and the reference standard on the same patients but it compared the results of CT colonography and colonoscopy performed on two different samples of patients (15) and it did not assess sensitivity and specificity.

5 studies were included (8,10,12,16,17). The results are reported in the table below.
The methodological quality of both systematic reviews and primary studies are quite good.
Both meta-analysis and primary studies reported accuracy data which are very heterogeneous: overall sensitivity is reported in two meta-analyses as 70% and 73& and ranges in primary studies from 26% to 62%. Overall specificity ranges in three meta-analyses from 77% to 100% and in primary studies from 45% to 94%. All meta-analysis and primary studies reported that sensitivity is low for small polyps and increase with polyp size. Incidences of adverse events is very low in all studies which assessed these outcomes. Three studies also reported patient preferences and found that participants prefer CT colonography over colonoscopy. None of the retrieved studies consider the possible damage associated with radiation.

CONCLUSIONS

Sensitivity of CT colonography is low for small polyps and increases with increasing polyp. All studies concluded that CT is not ready for routine use in clinical practice; before this screening method can be recommended for general use, it must be demonstrated to be highly and consistently sensitive in a variety of settings and questions about the optimal technological characteristics of the technique must be settled. (LEVEL OF EVIDENCE III)

Systematic reviews

Study	Bibliographic search	n. studies included	Overall sensitivity	Sensitivity for polyps <6mm	Sensitivity of polyps 6-10 mm	Sensitivity of polyps >10 mm	Sensitivity for cancer	Overall specificity	Specificity for polyps <6mm	Specificity polyps 6-10 mm	Specificity Polyps >10mm
Sosna 2003 (6)	MEDLINE, 1994- to July 2002	14 studies provided data on 1324 patients		65% (CI95% 57% - 73%)	84% (95%CI 80% to 89%)	88% (CI95% 84% to 93%)					95% (CI95%94% - 97%)
Halligan 2005 (3)	MEDLINE, EMBASE, Cochrane library 1994 - to December 2003	24 studies provided data on 4181 patients	Meta-analysis not performed because of statistical significant heterogeneity		Polyps 6-10 mm and >10 mm together 86% (CI95% 75%-93%)	93% (CI95% 73%-98%)	95% (CI95% 91.4% - 98.5%)	Meta-analysis not performed because of statistical significant heterogeneity		Polyps 6-10 mm and >10 mm together 86% (CI95% 76% - 93%)	97% (CI95%95%-99%)
Mulhall 2005 (2)	MEDLINE, EMBASE Cochrane Library January 1975 to February 2005	33 studies provided data on 6393 patients	70% (95% CI, 53% - 87%)	48% (CI, 25% to 70%)	70% (CI, 55% to 84%)	85% (CI, 79% to 91%)		86% (CI, 84% to 88%)	91% (CI, 89% to 95%)	93% (CI, 91% to 95%)	97% (CI, 96% to 97%)
Purkayastha 2006 (4)	MEDLINE, EMBASE, Up to November 2005	12 studies provided data on 1852 patients					96%	100% (for cancer)			

Study	Bibliographic search	n. studies included	Overall sensitivity	Sensitivity for polyps <6mm	Sensitivity of polyps 6-10 mm	Sensitivity of polyps >10 mm	Sensitivity for cancer	Overall specificity	Specificity for polyps <6mm	Specificity polyps 6-10 mm	Specificity Polyps >10mm
Walleser 2007 (7)	MEDLINE, Embase , Current Contents, Cochrane Library 1994- to June 2005	5 studies number of patients not reported				63% (95%CI, 55% - 71%)					95% (CI95%94% - 97%)
Rosman 2007 (5)	MEDLINE, 1996- to November 2005	30 studies provided data on 6596 patients	73% (CI95% 66% - 81%)	56% (CI95% 42% - 70%)	63% (CI95% 52% - 75%)	82% (CI95% 76% -88%)		77% (CI95% 69% - 86%)			96% (CI95%95% - 97%)
Whitlock 2008 (1)	Medline, Cochrane library 1999- january 2008	2 studies			Polyps 6-10 mm and >10 mm together 88.7% (C95% 82.9–93.1)	92 % (CI95% 88%–96%)				Polyps 6-10 mm and >10 mm together 79.6% (CI95%77.0–82.0)	96% (CI95% 94.8–97.1)

Primary studies

Study	Participants	Overall sensitivity	Sensitivity for polyps <6mm	Sensitivity of polyps 6-10 mm	Sensitivity of polyps >10 mm	Sensitivity for cancer	Overall specificity	Specificity for polyps <6mm	Specificity polyps 6-10 mm	Specificity Polyps >10mm
Arnesen 2007 (8)	231	60% (95% CI, 50% - 70%)		Polyps 6-10 mm and >10 mm together 69% (95%CI 58% - 80%)	81% (95%CI 68% - 94%)	80% (4/5)	78% (95%CI 70% to 86%)		Polyps 6-10 mm and >10 mm together 91% (95%CI 84% - 98%)	98% (95%CI 93% to 100%)
Chaparro 2007 (10)	50	26%	6%	75%	80%		94%	94%	89%	100%
Jensch 2008 (12)	168	60% (CI95% 50% - 70%)		71% (CI95% 55%- 88%)	82% (CI95% 64% -100%)				81% (CI95% 74% - 87%)	97% (CI95% 94%-100%)
Reuterskiold 2006 (16)	114		59%	56%	95%		45%			92%
Roberts-Thomson 2008 (17)	202	62% (95% CI, 50%-74%)		Polyps 6 to 9 mm and larger than 10 mm together: 78% (95% CI, 58%-91%)		55.5%	76% (95% CI, 67%-83%),		Polyps 6 to 9 mm and larger than 10 mm: 82% (95% CI, 76%-88%)	

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1.9.2 Evidence tables

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Whitlock 2008	To assess the accuracy and potential harms of newer colorectal cancer screening tests (high-sensitivity FOBTs, faecal immunochemical tests, faecal DNA testing, and CT colonography) Reference standard: colonoscopy	Systematic review PubMed; DARE; CDSR; Institute of Medicine, National Institute for Health and Clinical Effectiveness, and Health Technology Assessment databases for recent systematic reviews (1999 –2006) MEDLINE and Cochrane January 2006 through January 2008 to locate additional studies published after the end date of the searches.	DNA testing: 1 study (Imperiale 2004) on 4404 average risk persons already considered by our review Immunochemical test: 9 studies on 86498 average risk persons CT colonography: 7 studies located, 4 included on 4312 average-risk patients	Sensitivity specificity	**Immunochemical tests** had higher sensitivity for colorectal cancer (61% to 91%) than was reported for non rehydrated Hemoccult II (25% to 38%) Estimated specificity varied across faecal immunochemical tests (91% to 98%), and, in most studies, specificity appears lower than the reported specificity of non rehydrated Hemoccult II (98% to 99%) **DNA testing:** Onetime faecal DNA testing was more sensitive for adenocarcinoma than was Hemoccult II (sensitivities of 51% [CI, 34.8% to 68.0%] and 12.9% [CI, 5.1% to 28.9%], respectively). Both faecal DNA testing and Hemoccult II had poor sensitivity for advanced carcinoma. **CT colonography** Results from the two larger and high quality studies (Pickhardt 2003, Johnson 2008) <u>Sensitivity</u> Adenoma ≥ 10 mm 92 % (CI95% 88%–96%) Adenoma ≥ 6 mm 88.7% (C95% 82.9–93.1) <u>Specificity</u> Lesion ≥ 10 mm 96% (CI95% 94.8–97.1) Lesion ≥ 6 mm 79.6% (CI95%77.0–82.0) Sensitivity and specificity estimates from 2 smaller fair quality studies comparing CT colonography with colonoscopy (Kim 2007, Johnson 2007) are less informative because these studies detected relatively few lesions and their primary purposes were:	**III** **Immunochemical tests** had superior single test sensitivity for colorectal cancer and possibly for advanced neoplasia compared with Hemoccult II. Faecal immunochemical tests had similar or somewhat lower specificity, **DNA testing:** showed improved sensitivity for colorectal cancer but not adenomas, similar or slightly reduced specificity, and higher positive rates ompared with Hemoccult II. This study's findings may not be generalisable to population screening because participants were relatively older (three quarters were _65 years of age, compared with screening beginning at age 50 years) and the version of PreGen Plus tested has been supplanted by other versions for which there are no screening population studies. **CT colonography** screening by trained and experienced radiologists had sensitivity similar to that of colonoscopy for colorectal cancer and large adenomas (≥10 mm).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
					1) to examine the relative accuracy of 2-dimensional vs. 3-dimensional methods for displaying and reviewing CT colonography images and 2) to compare radiologist performance Thus, these studies do not provide overall results for the population but rather report subsets of data to compare readers or technologies. Results are generally consistent, with better sensitivity for larger (compared with smaller) lesions, no clear differences between 2- and 3-dimensional approaches.	However, estimates of sensitivity of CT colonography for smaller adenomas (≥6 mm) was more variable between studies. Other uncertainties may affect considerations of whether this test is ready for widespread population screening. These include questions about potential harms from radiation exposure, uncertainty about extracolonic findings, uncertainty about test referral thresholds and repeat test intervals, and judgments about how the test performance seen in clinical studies will translate to the conduct of CT colonography screening examinations in community settings.

Quality assessment: more than one database searched. Publication bias: not specified if only English language studies considered. Selection of studies, data abstraction done by two independent reviewers. Quality assessment of primary studies done. Trial flow reported Characteristic of included studies reported.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Mulhall 2005	To Systematically review the test performance of CT colonography compared to colonoscopy . Study Selection: Prospective studies of adults undergoing CT Reference standard: colonoscopy or surgery	Systematic review MEDLINE, EMBASE Cochrane Library January 1975 to February 2005	33 studies provided data on 6393 patients Mean age of participants 61.9 years; Male: 63.6% .At high risk for colorectal cancer: 74%. 16 studies used single detector scanners, 13 used multidetector scanners, and 4 used both single-detector and multidetector scanners. 15 used 2-dimensional imaging, with 3-dimensional imaging on selected slices at the discretion of the radiologist; 14 studies used dedicated 2-dimensional and 3-dimensional imaging; and 2 studies used fly-through imaging with 2-dimensional reconstruction. The average collimation was 4 mm (range, 1 to 5 mm), and the average reconstruction interval was 1.86 mm (range, 1 to 5 mm).	Sensitivity Specificity for polyp detection	**Overall sensitivity**: 70% (95% CI, 53% - 87%) Sensitivity increased progressively as polyp size increased: **Polyps smaller than 6 mm**: 48% (CI, 25% to 70%) **Polyps 6 to 9 mm:** 70% (CI, 55% to 84%) **Polyps larger than 9 mm**: 85% (CI, 79% to 91%) Each of these analyses was statistically heterogeneous (P <0.001 for each) Several potential sources for this heterogeneity have been found: 1. thinner slices for collimation appeared to have better sensitivity, and meta-regression of data from 19 studies suggested that every 1-mm increase in collimation width decreases sensitivity by 4.9% (CI, 0.8% to 7.1%). 2. multidetector scanners had homogenously higher sensitivity (95% [CI, 92% to 99%]; I2: 40%; P >0.2) than scanner with a single-detector (82% [CI, 76% to 92%]), although the latter results were heterogeneous (I2:87.1%; P <0.001). 3. 2-dimensional imaging, with confirmation by 3-dimensional imaging only when considered necessary, yielded a sensitivity of 81.9% (CI, 71% to 91%) (I2: 87.5%; *P: 0.02*), standard 2-dimensional imaging and concomitant 3-	**III** CT colonography is highly specific, particularly for polyps greater than 9 mm in size. However, the reported sensitivities for CT colonography vary widely, even for larger polyps. Before any screening method can be recommended for general use, it must be demonstrated to be highly and consistently sensitive in a variety of settings. The inability of our meta-analysis to clearly explain why the reported sensitivities vary so widely suggests that CT colonography needs further refinement before it can be recommended for general use in screening for colorectal cancer. Our analysis revealed some factors that account for the wide range of sensitivities. First, scanners that used thinner collimation had higher sensitivity. Every 1-mm increase in collimation width decreased the subsequent sensitivities by almost 5%. That is, if scanners with 1-mm slices had 98% sensitivity, increasing the collimation width to 2 mm would decrease sensitivity to 93%. Second, scanners that used

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
					dimensional imaging had a pooled sensitivity of 91% (CI, 83% to 99%) (I2 : 53.1%; *P* :0.06) and fly-through technology had a pooled sensitivity of 99% (CI, 95% to 100%) (I2 :47.6%; *P* :0.17) **Overall specificity**: 86% (CI, 84% to 88%) (I2 : 92.6%; *P* <0.001) **Polyps smaller than 6 mm**: 91% (CI, 89% to 95%) (I2: 47.1%; *P:* 0.15). **Polyps 6 to 9 mm**: 93% (CI, 91% to 95%) (I2 : 50%; *P :* 0.07 **Polyps larger than 9 mm**: 97% (CI, 96% to 97%) (I2 :41.8%; *P:_* 0.2)	multiple detectors rather than single detectors were more sensitive. Finally, the mode of imaging also appeared to be important: The more recently developed fly-through technology had a sensitivity of 99%. These results suggest that CT colonography is promising as a screening test for colorectal cancer. Before it is put into general use, however, it must be shown to be reliably sensitive and questions about the optimal technological characteristics of the technique must be settled.

Quality assessment: more than one database searched. Publication bias: only English language studies considered. Selection of studies, data abstraction done by two independent reviewers. Quality assessment of primary studies done. Trial flow reported Characteristic of included studies reported. Statistical heterogeneity assessed and sources of heterogeneity by performing stratified analyses when the potential confounding variable was dichotomous or categorical, by plotting the weighted effect size against the potential confounding variable when that variable was continuous, and by applying meta-regression methods in either case . Subgroup analyses were done by year of publication, imaging technique (2-dimensional imaging with 3-dimensional confirmation only when a lesion was noted, 3-dimensional imaging with 2-dimensional confirmation, 2-dimensional imaging with concomitant 3-dimensional imaging, or fly-through technology), collimation width and reconstruction interval (in millimeters), type of scanner (single-detector, multidetector, or mixed), and use of a contrast agent (yes or no).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Halligan 2005	To Systematically review the test performance of CT colonography compared to colonoscopy. Study Selection: Prospective studies of adults undergoing CT Reference standard: colonoscopy or surgery	Systematic review MEDLINE, EMBASE, Cochrane library 1994- to December 2003	24 studies provided data on 4181 patients	Sensitivity Specificity for polyp detection	**Large polyps alone (1 cm or more)** 2610 patients from 7 studies Sensitivity: 93% (CI95% 73%-98%) Specificity: 97% (CI95%95%-99%) **Medium (between 6 and 9 mm) and large polyps (larger than 5mm)** 1834 patients from 7 studies Sensitivity: 86% (CI95% 75%-93%) Specificity: 86% (CI95% 76% - 93%) **All polyps (smaller than 6 mm, medium and large** 1361 patients from 12 studies Meta-analysis not performed because of statistical significant heterogeneity **Cancer**: 95% (CI95% 91.4% - 98.5%)	**III** CT colonography seems sufficiently sensitive and specific in the detection of large and medium polyps.

Quality assessment: more than one database searched. Publication bias: no language restriction. Selection of studies and data abstraction done by two independent reviewers. Quality assessment of primary studies done. Trial flow reported Characteristic of included studies reported. Reason for exclusion reported. Statistical heterogeneity assessed.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Purkayastha 2007	To Systematically review the test performance of CT colonography compared to colonoscopy. Study Selection: Prospective studies of adults undergoing CT Reference standard: colonoscopy	Systematic review MEDLINE, EMBASE, Up to November 2005	12 studies provided data on 1852 patients	Sensitivity Specificity for cancer detection Area under the SROC curve	Overall sensitivity: 96% no significant heterogeneity Overall specificity: 100% no significant heterogeneity AUC: 0.99%	III

Quality assessment: more than one database searched. Publication bias: no language restriction. Selection of studies and data abstraction done by three independent reviewers. Quality assessment of primary studies done. Trial flow reported. Characteristics of included studies reported. Reason for exclusion reported. Statistical heterogeneity assessed. Subgroup analysis performed for publication date (before and after 2003), study quality (over or above a score of 18 at the STARD checklist.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Rosman 2007	To Systematically review the test performance of CT colonography compared to colonoscopy. Study Selection: Prospective studies of adults undergoing CT Reference standard: colonoscopy	Systematic review MEDLINE, 1996- to November 2005	30 studies provided data on 6596 patients	Sensitivity Specificity for polyp detection	Sensitivity **Overall**: 73% (CI95% 66% - 81%) **Polyps smaller than 6 mm**: 56% (CI95% 42% - 70%) **Polyps 6 to 10 mm** : 63% (CI95% 52% - 75%) **Polyps larger than 10 mm**: 82% (CI95% 76% - 88%) Specificity: **overall:** 77% (CI95% 69% - 86%) **Polyps larger than 10 mm** 96% (CI95%95% - 97%)	**III** CT colonography has a reasonable sensitivity and specificity for detecting large polyps but was less accurate than colonoscopy for smaller polyps. Thus, CT colonography may not be a reasonable alternative in situations in which a small polyp may be clinically relevant.

Quality assessment: only one database searched. Publication bias: not specified if language restriction was used. Not specified if selection of studies and data abstraction were done by two independent reviewers. Quality assessment of primary studies not done. Trial flow not reported Characteristic of included studies reported. Reason for exclusion not reported. Statistical heterogeneity not assessed.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Sosna 2003	To Systematically review the test performance of CT colonography compared to colonoscopy. Study Selection: Prospective studies of adults undergoing CT Reference standard: colonoscopy	Systematic review MEDLINE, 1994- to July 2002	14 studies provided data on 1324 patients	Sensitivity Specificity for polyp detection	Sensitivity **Polyps smaller than 6 mm**: 65% (CI95% 57% - 73%) **Polyps 6 to 10 mm** : 84% (95%CI 80% to 89%) **Polyps larger than 10 mm**: 88% (CI95% 84% to 93%) Specificity: **Polyps larger than 10 mm** 95% (CI95%94% - 97%)	**III** CT colonography appears to be an accurate tool for detecting clinically important colorectal polyps. The specificity and sensitivity of CT colonography are especially good for detecting polyps 10 mm or larger.

Quality assessment: only one database searched. Publication bias: only English language study selected. Selection of studies and data abstraction done by two independent reviewers. Quality assessment of primary studies not done. Trial flow not reported Characteristic of included studies reported. Reason for exclusion reported. Statistical heterogeneity assessed.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Walleser 2007	To Systematically review the test performance of CT colonography compared to colonoscopy. Study Selection: Prospective studies of adults undergoing CT because of symptoms or high risk family history. Reference standard: colonoscopy	Systematic review MEDLINE, Embase , Current Contents, Cochrane Library 1994- to June 2005	5 studies number of patients not reported	Sensitivity Specificity for polyp greater that 10mm detection in non screening population	Sensitivity **Polyps larger than 10 mm**: 63% (CI, 55% to 71%) Specificity: **Polyps larger than 10 mm** 95% (CI95%94% - 97%)	**III** CT colonography appears less accurate than colonoscopy in detecting polyps greater than 10 mm

Quality assessment: more than one database searched. Publication bias: only English language study selected. Selection of studies and data abstraction done by one reviewer and checked by a second reviewer. Quality assessment of primary studies done. Trial flow reported Characteristic of included studies reported. Reason for exclusion reported. Statistical heterogeneity assessed.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Arnesen 2007	To assess the test performance of CT colonography compared to colonoscopy . Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study	231 consecutive patients referred for colonoscopy because of polyp surveillance (39%), post CRC surveillance (35%), alarm sign or symptoms. Patients with acute symptoms, recent abdominal surgery, colostomy, pregnancy, or failure to fulfil the bowel preparation regimen were excluded.	Sensitivity Specificity for polyp detection	**Overall sensitivity**: 60% (95% CI, 50% - 70%) **Polyps greater than 5 mm**: 69% (95%CI 58% - 80%) **Polyps larger than 10mm**: 81% (95%CI 68% - 94%) **Sensitivity for cancer**: 80% (4/5 CRC detected) **Overall specificity**: 78% (95%CI 70% to 86%) **Polyps greater than 5 mm**: 91% (95%CI 84% - 98%) **Polyps larger than 10 mm**: 98% (95%CI 93% to 100%) No patient asked for the CTC to be terminated because of discomfort or pain, and there were no clinically significant adverse events.	**III** The diagnostic performance of CTC was inferior to that of CC for lesions >5 mm, but comparable for lesions >10 mm. CC was superior to CTC and should remain first choice for the diagnosis of colorectal polyps. However, for diagnosis of lesions >10 mm, CTC and CC should be considered as complementary methods

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test and reference test results interpreted without knowledge of the results of the other test. Execution of index test, comparator and reference standard clearly described. The entire selected sample received reference standard (avoidance of selection bias).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Chaparro 2007	To assess the test performance of CT colonography compared to colonoscopy . Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study	50 consecutive patients referred for colonoscopy because alarm sign or symptoms or history of colorectal polyps. . Exclusion criteria were as follows: age <18 years, inability to give written consent, refusal to participate, prior colorectal surgery, diagnosis of inflammatory bowel disease, contraindications for a CC, and pregnancy	Sensitivity Specificity for polyp detection	**Overall sensitivity**:26% **Polyps smaller than 5 mm** :6% **Polyps 5 to 10 mm** 75% **Polyps larger than 10 mm**: 80% **Overall specificity**: 94% **Polyps smaller than 5 mm**: 94% (CI, 25% to 70%) **Polyps 5 to 10mm** 89% (CI, 55% to 84%) **Polyps larger than 10 mm**: 100% (CI, 79% to 91%) Participants mostly preferred virtual colonoscopy (90%), over conventional colonoscopy. The tolerance of patients was good in all patients.	**III** The sensitivity of CTC is moderate in detecting polyps larger than 10 mm, low in detecting 5-10 mm polyps and very low in detecting those less than 5 mm. Procedure time was lower with CC than with CTC but the latter was better tolerated by most patients. Our results indicate that CTC using these techniques is not ready for routine use as a tool at this time. For the time being, CTC should be used in research protocols or when other accepted diagnostic methods, such as CC, are not appropriate.

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test and reference test results interpreted without knowledge of the results of the other test. Execution of index test, comparator and reference standard clearly described .All patients performed colonoscopy (absence of verification bias).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Jensch 2008	To assess the test performance of CT colonography compared to colonoscopy . Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study	174 patients at increased risk for personal or family history. 168 included in the analysis Exclusion criteria were age younger than 18 years, a personal history of inflammatory bowel disease or familial adenomatous polyposis, prior allergic reaction to an iodine-containing contrast agent, known colorectal polyps that were not removed at prior endoscopy	Sensitivity Specificity for polyp detection	**Overall sensitivity**: 60% (CI95% 50% - 70%) **Polyps 6 to 9 mm:** 71% (CI95% 55%-88%) **Polyps larger than 9 mm**: 82% (CI95% 64% -100%) **Overall specificity**: not reported **Polyps 6 to 9 mm** 81% (CI95% 74% - 87%) **Polyps larger than 9 mm**: 97% (CI95% 94%-100%) Patient preference: 70% of patients preferred CT colonography to colonoscopy, 8% were indifferent, and 22% favoured colonoscopy.	**III**

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test interpreted without knowledge of the results of the reference standard. Results of the reference standard interpreted with knowledge of the CT colonography results (unblinding). Execution of index test, comparator and reference standard clearly described. 6 patients excluded from the analysis; reason for exclusion given.

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Reuterskiold 2006	To assess the test performance of CT colonography compared to colonoscopy . Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study	114 patients at increased risk for personal history or alarm symptoms and signs. Exclusion criteria Women younger than 50 years of age and patients with acute colitis or colostomy	Sensitivity Specificity for polyp detection	**Sensitivity** **Polyps <5 mm:** 59% **Polyps 5 to 9 mm** 56% **Polyps larger than 10 mm**: 95% **Overall specificity**: 45% (CI95% 34%-57%) **Polyps larger than 10 mm**: 92% (CI95% 85%-96%)	**III** CT colonography had a high sensitivity for lesions >5 mm. The diagnostic performance increased with lesion size

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test interpreted without knowledge of the results of the reference standard. Results of the reference standard interpreted with knowledge of the CT colonography results (unblinding). Execution of index test, comparator and reference standard clearly described. All patients underwent colonoscopy (absence of verification bias).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Roberts-Thomson 2008	To assess the test performance of CT colonography compared to colonoscopy . Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study	227 patients with alarm symptoms and signs, family history of colorectal cancer , previous colonic polyps or a recent positive faecal occult blood test Exclusion criteria included inflammatory bowel disease and major coexisting medical disorders. Data reported for 202 patients who performed a complete colonoscopy	Sensitivity Specificity for polyp detection	**Overall Sensitivity:** 62% (95% CI, 50%-74%) **Polyps 6 to 9 mm** and **larger than 10 mm together:** 78% (95% CI, 58%-91%) **Sensitivity for cancer**: 55.5% **Overall specificity**: 76% (95% CI, 67%-83%), **Polyps 6 to 9 mm** and **larger than 10 mm**: 82% (95% CI, 76%-88%) Patients preference: when asked to choose between CT colonography and colonoscopy for a repeat procedure, 61% chose CT colonography and 39% chose colonoscopy	**III** Although CT colonography was more sensitive in this study than in some previous studies, the procedure is not yet sensitive enough for widespread application in symptomatic patients Although CT colonography is not yet ready for widespread clinical application, it is likely that results will improve with better bowel preparation, technical developments and increasing familiarity with the technique.

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test interpreted without knowledge of the results of the reference standard. Results of the reference standard interpreted with knowledge of the CT colonography results (unblinding). Execution of index test, comparator and reference standard clearly described. 89% of patients performed colonoscopy; reason for exclusion reported.

1.10 Efficacy and diagnostic accuracy of capsule endoscopy

1.10.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 13

Is Capsule Endoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Capsule endoscopy screening test
C: No screening
O: Colorectal cancer incidence, colorectal cancer mortality
S: (Systematic reviews of) RCTs, cohort- and case-control studies

CLINICAL QUESTION 13B

Is capsule endoscopy comparable to colonoscopy in test performance characteristics (sensitivity and specificity)?

PICOS

P: Asymptomatic population
I: Capsule endoscopy
C: Colonoscopy
O: 1. Sensitivity/ detection rate. 2. Specificity
S: (Systematic reviews of) diagnostic accuracy studies

SEARCH METHOD

Clinical question 13

Search strategy for primary studies
("Capsule Endoscopy"[Mesh] OR capsule endoscopy) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND systematic[sb]

Limits: Humans, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years

Search strategy for systematic reviews
("Capsule Endoscopy"[Mesh] OR capsule endoscopy) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND systematic [sb]

Limits: Humans, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years

Clinical question 13b

Search strategy for primary studies
(specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*) AND (("Colonoscopy"[Mesh] OR colonoscopy) AND ("Capsule Endoscopy"[Mesh] OR capsule endoscopy))

Search strategy for systematic reviews
(Specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*) AND (("Colonoscopy"[Mesh] OR colonoscopy) AND ("Capsule Endoscopy"[Mesh] OR capsule endoscopy)) AND systematic [sb]

RESULTS

Only four studies have been retrieved. One was a systematic review published in 2007 (1), one was a narrative review published in 2007 (2) and two were primary studies assessing the accuracy of capsule endoscopy (3,4). No studies were retrieved assessing the effectiveness of capsule endoscopy in reducing colorectal cancer mortality or incidence. A systematic review published in 2003 was retrieved but not considered because it was out of date (5).

The two reviews included the two primary studies also retrieved by our search, and are the only studies already published. The systematic review by Tran 2007 is based on a bibliographic search from 2002 to 2007, but the search strategy and the databases searched are not reported. The review by Fireman 2007 reports the preliminary findings of two ongoing trials: the USA trial (presented at the meeting of the American College of Gastroenterology Las Vegas, NE, USA, October 2006) included 51 subjects and compared capsule colonoscopy, standard colonoscopy and virtual colonoscopy. The sensitivity was 79% for the capsule, 89% for conventional colonoscopy and 32% for CT colonography. The specificity of the capsule was, however, only 53%, compared to the 97% and 100% for CT colonography and standard colonoscopy, respectively. The review did not report the reference standard used in the study. An eight centre European study targeted 329 patients for a double blind study comparing standard colonoscopy to Pill Cam TM Colon capsule endoscopy, and initial data are already available on 84 patients (presented at the Digestive Disease Week Meeting, Washington DC, USA, May 2007). The capsule had a sensitivity of 79% and a specificity of 78% for the detection of polyps. A seven-centre USA trial targeted 340 subjects and was designed to evaluate and compare the accuracy and safety of Pill Cam TM Colon capsule endoscopy for patients with significant findings on standard colonoscopy. It was also cited but interim results are not reported.

The two completed trials (3,4) assessed the accuracy of capsule endoscopy using colonoscopy as a reference standard on 36 and 86 patients, respectively. They were both of good methodological quality and employed patients representative of the patients who will receive the test in practice (undergoing colonoscopy as a screening test or for alarm symptoms). The reported sensitivity was 76% and 56%, the reported specificity was 64% and 69%. No capsule endoscopy-related adverse effects were reported in either of the two studies.

CONCLUSIONS

Capsule endoscopy should be considered as a promising new alternative technology to colonoscopy; the benefits of the colon capsule could be that the examination can be realised without intubation, insufflation, pain, sedation, and radiation; no serious adverse effects have been reported. The data about accuracy are less satisfactory compared to colonoscopy. They come only from two small pilot trials and further studies are needed before implementing this new method in general practice. (LEVEL OF EVIDENCE III)

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1.10.2 Evidence tables

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Eliakim 2006	Capsule endoscopy Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study Israeli	91 patients scheduled for screening colonoscopy, post polypectomy surveillance, or for alarm symptoms. Final data allowable for 84 patients	Sensitivity Specificity PPV NPV	7 patients excluded: one could not swallow the capsule because of anxiety, two failed to adhere to the colon preparation, in one patient the capsule remained in the stomach, and in three there was a technical capsule failure. Sensitivity: 54% Specificity: 69% PPV: 57% NPV: 67%	III Capsule endoscopy appears to be a promising new modality for colonic evaluation. Additional studies are needed to evaluate the accuracy of the capsule in other populations with different prevalence of colonic disease

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test and reference test results interpreted without knowledge of the results of the other test. Execution of index test, comparator and reference standard clearly described. Drop out from the study described and reason given. The entire selected sample received reference standard (avoidance of selection bias).

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schoofs 2006	Capsule endoscopy Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study Belgium	41 patients scheduled for screening colonoscopy with or without personal or family history of CRC or for alarm symptoms. Final data allowable for 36 patients	Sensitivity Specificity PPV NPV Interobserver agreement with regard to significant lesions	Five patients were excluded, one could not swallow the capsule because of anxiety, in four patients because of technical problems related to the capsule Sensitivity: 76% Specificity: 64% PPV: 83% NPV: 54% Interobserver agreement: 83.5%	**III** Capsule endoscopy showed promising accuracy results compared to colonoscopy. This new non invasive technique deserves further evaluation as a potential CRC screening tool

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test and reference test results interpreted without knowledge of the results of the other test. Execution of index test, comparator and reference standard clearly described. Drop out from the study described and reason given. The entire selected sample received reference standard (avoidance of selection bias).

1.11 Colorectal cancer screening cost effectiveness

1.11.1 Summary document

Rita Banzi

CLINICAL QUESTION 14A

Is guaiac FOBT screening offered to the general population age 50 and older cost-effective?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Guaiac FOBT screening test
C: No screening
O: Discounted cost per life-year gained
S: (Systematic reviews of) cost-effectiveness analyses

CLINICAL QUESTION 14B

Is immunological/immunochemical FOBT screening offered to the general population age 50 and older cost-effective?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Immunochemical FOBT screening test
C: No screening
O: Discounted cost per life-year gained
S: (Systematic reviews of) cost-effectiveness analyses

CLINICAL QUESTION 14C

Is flexible sigmoidoscopy screening offered to the general population age 50 and older cost-effective?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Flexible sigmoidoscopy screening test
C: No screening
O: Discounted cost per life-year gained
S: (Systematic reviews of) cost-effectiveness analyses

CLINICAL QUESTION 14D

Is colonoscopy screening offered to the general population age 50 and older cost-effective?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Colonoscopy screening test
C: No screening
O: Discounted cost per life-year gained
S: (Systematic reviews of) cost-effectiveness analyses

SEARCH METHOD

We updated the search strategy used by Pignone et al.in their systematic review (1) and we searched MedLine from 2001 using the following Mesh terms: "colorectal neoplasms", "mass screening" and "costs and cost analysis".

We also searched The Cochrane Library in order to retrieve additional papers and the structured abstracts of the relevant publications.

RESULTS

Overall, we found six cost effectiveness analyses relevant for this topic (2-7) and not included in the above mentioned systematic review(1).

Different type of screening (Faecal Occult Blood test-FOBT, sigmoidoscopy, colonoscopy).

One systematic review (1) and three subsequent RCTs (2-4) compared the cost effectiveness of the following CRC screening strategies: biennial FOBT, sigmoidoscopy, FOBT and sigmoidoscopy, colonoscopy. The investigated interval was slightly different across studies. The systematic review by Pignone included seven cost effectiveness analyses, five examined multiple CRC screening strategies and 2 examined single strategies. All the cost effectiveness models were performed in the United States and referred to a cohort of adults at average risk aged between 50 and 85 years of age. All studies found that screening for CRC by any of the included screening strategies (annual FOBT, sigmoidoscopy every 5 years, combination of annual FOBT and sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, colonoscopy every 10 years, at 55 and 65 years of age, or once in a lifetime) reduced deaths from CRC. In base-case analysis most strategies had average cost-effectiveness ratios ranging from $ 10,000 to 25,000 per year of live saved. The most effective strategy tended to be colonoscopy every 10 years or the combination of annual FOBT + sigmoidoscopy every 5 years. However, whether one method is superior to the others was not clear. One of the studies included in the above-mentioned review (8) was updated in a subsequent publication (2) which confirmed a clinically preventable burden measured as life year saved (LYS) (338,000 compared to 325,000 LYS) and a small increase in the cost-effectiveness ratio in nominal terms ($11,900/LYS in year 2000 dollars compared to $11,800/LYS in 1995 dollars).

Annual and biennial FOBT, sigmoidoscopy every 10 years, and colonoscopy every 10 years were compared with no screening in an Australian study performed on a cohort of asymptomatic, average-risk individuals aged 55–64 years who were moving through a defined series of states towards death. (3) The incremental cost per life-year saved by flexible sigmoidoscopy screening was A$16 801 compared with no screening, which was considered cost-effective in terms of health interventions. Colonoscopy screening was also cost-effective while both biennial and annual FOBT screening were less cost-effective. Very similarly, a study conducted in the US compared five alternative screening strategies for CRC with no screening (biennial FOBT for individuals aged 50 to 69 years; biennial FOBT for individuals aged 60 to 69 years; once only flexible sigmoidoscopy (FS) for individuals aged 55 years; once only FISG for individuals aged 60 years; and once only FS for individuals aged 60,

followed by biennial FOBT for individuals aged 61 to 70 years)(4). This study showed that screening using FOBT and/or flexible sigmoidoscopy are potentially cost-effective strategies for the early detection of CRC.

FOBT

Three cost effectiveness studies specifically investigated FOBT screening (5-7). The first one estimated the cost-effectiveness of biennial FOBT screening over up to five screening rounds within the Nottingham trial, a randomised controlled trial of 153,000 subjects aged from 45 to 74 years(5) .The FOBT screening programme was cost-effective over no screening. The cost of screening was 5,290 pound per cancer detected (at 2002 prices). Under conservative assumptions, the incremental cost per life year gained as a result of screening was 1,584 pound (95% CI: 717 to 8,612).

A French cost effectiveness analysis on a hypothetical cohort of 100,000 asymptomatic individuals aged 50 to 74 years confirmed that a biennial FOBT was a cost-effective screening strategy for CRC. (6) Incremental LYGs of screening over no screening were EUR 3,375 (2,492 if undiscounted) and EUR 4,705 (4,007 if undiscounted) with a 20 and 10 years time horizon, respectively.

We were unable to retrieve studies specifically addressing cost effectiveness of immunochemical-FOBT. One French analysis compared costs and the effectiveness of 20 years of biennial CRC screening performed with an automated reading immunological test (Magstream) and guaiac stool test (Hemoccult)(7). The use of Magstream for 20 years of biennial screening, costs 59 euros more than Hemoccult per target individual, and should lead to a mean increase in individual life expectancy of 0.0198 years (i.e. about one week), which corresponds to an incremental cost-effectiveness ratio of 2980 euros per years of life saved. Thus, these results suggest that using an immunological test could increase the effectiveness of CRC screening at a reasonable cost.

CONCLUSIONS

From the evidence retrieved it appears that CRC screening is cost effectiveness but a single optimal strategy cannot be determined. Due to the large differences among studies in terms of perspective, setting, country, and quality is difficult to draw general conclusions on the cost effectiveness of CRC screening. We included cost effectiveness studies performed in the Western countries: although some of these were European (France, UK), resource use and costs are sensitive to variability across setting and local context thus limiting the generalisability and transferability of estimates across different countries. Moreover, the most "cost-effective" strategy identified depended on the level of incremental cost-effectiveness considered.

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1.11.2 Evidence tables

Author, publication year	Intervention	Study design	Participants/ Setting	Outcome	Results	Level of evidence Conclusions
Pignone 2002	Annual FOBT, sigmoidoscopy every 5 years, combination of annual FOBT and sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, colonoscopy (every 10 years, at 55 and 65 years of age, or once in lifetime). Each model used data on the incidence of CRC neoplasm (adenomatous polyps and cancer) to simulate the natural history of the disease	Systematic review of cost effectiveness analysis	7 studies were included: 5 examined multiple CRC screening strategies and 2 examined single strategies Cost effectiveness models on a cohort of adults at average risk aged between 50 and 85 years of age Perspective: societal and third part payer United States	Benefits of different screening strategies presented in days of life or life-years gained and costs in US dollars. Most effective strategy (defined as that yielding the greatest average number of life-years gained). Most "cost-effective" strategy (which depends on the cost threshold beyond which one no longer wishes to "pay" for additional years of life saved)	***Cost-Effectiveness Ratios of Different Tests for CRC vs. No Screening ($)*** <u>Annual FOBT</u> Wagner 1996: 11 725 Frazier 2000: 17 805 Khandker 2000: 13 656 Sonnenberg 2000: 10 463 Vijan 2001: 5691 <u>FS every 5 years</u> Wagner 1996: 12 477 Frazier 2000: 15 630 Khandker 2000: 12 804 Sonnenberg 2000: 39 359 Vijan 2001: 19 068 <u>Annual FOBT+FS every 5 years</u> Wagner 1996: 13 792 Frazier 2000: 22 518 Khandker 2000: 18 693 Sonnenberg 2000: - Vijan 2001: 17 942 <u>DCBE every 5 years</u> Wagner 1996: 11 168 Frazier 2000: 21 712 Khandker 2000: 25 624 Sonnenberg 2000: - Vijan 2001: - <u>Colonoscopy every 10 years</u> Wagner 1996: 10 933 Frazier 2000: 21 889 Khandker 2000: 22 012 Sonnenberg 2000: 11 840 Vijan 2001: 9038	All studies found that screening for CRC by any of the included screening strategies reduced deaths from CRC in adults older than 50 years of age and at average risk. In base-case analysis most strategies had average cost-effectiveness ratio ranging from $ 10000 to 25000 per year of live saved. Whether one method is superior to others is not clear: the most effective strategy tended to be colonoscopy every 10 years or the combination of annual FOBT + FS every 5 years. The most "cost-effective" strategy identified depended on the level of incremental cost-effectiveness considered to be worthwhile and was not conclusive

Author, publication year	Intervention	Study design	Participants/ Setting	Outcome	Results	Level of evidence Conclusions
					Most effective strategy Wagner 1996: annual FOBT+FS every 5 yrs Frazier 2000: annual FOBT+FS every 5 yrs Vijan 2001: annual FOBT+FS every 5 yrs Khandker 2000: colonoscopy every 10 Sonnenberg 2000: colonoscopy every 10 (this study did not consider the combination annual FOBT+FS every 5 yrs) ***Most cost-effective strategy*** <u><$ 20000 per life-year saved</u> Wagner 1996: colonoscopy every 10 years Frazier 2000: annual FOBT Khandker 2000: FS every 5 years Sonnenberg 2000: colonoscopy every 10 years Vijan 2001: annual FOBT <u>$ 20000-30000 per life-year saved</u> Wagner 1996: colonoscopy every 10 years Frazier 2000: annual FOBT Khandker 2000: FS every 5 years Sonnenberg 2000: colonoscopy every 10 years Vijan 2001: annual FOBT <u>$ 30000-50000 per life-year saved</u> Wagner 1996: annual FOBT+FS every 5 years Frazier 2000: annual FOBT+FS every 5 years Khandker 2000: annual FOBT Sonnenberg 2000: colonoscopy every 10 years Vijan 2001: colonoscopy only at 55 and 65 yrs <u>$ 50000-100000 per life-year saved</u> Wagner 1996: annual FOBT+FS every 5 years Frazier 2000: annual FOBT+FS every 5 years Khandker 2000: colonoscopy every 10 years Sonnenberg 2000: colonoscopy every 10 years Vijan 2001: colonoscopy only at 55 and 65 yrs	

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE AND THE BRITISH NATIONAL HEALTH SERVICE ECONOMIC EVALUATION DATABASE (1966-6/2002); MANUALLY SEARCH OF REFERENCES OF RETRIEVED STUDIES CONTACT WITH AUTHORS AD EXPERT IN THE FIELD
	Date restriction	January 1993-September 2001
	Any restriction	-
Selection	Inclusion and exclusion criteria	The following studies were excluded: cost-effectiveness or cost-utility analyses, including other types of economic evaluations that did not quantify the health outcomes achieved for a given cost; studies that reported only cost per patient screened, cost per cancer detected, or cost per death prevented; studies that did not contain original analyses; studies performed from perspectives other than the societal perspective or the perspective of public third-party payers; and studies that used cost or disease incidence estimates from outside the United States.
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	All authors reviewed each included article. Reviews focused on the assumptions of each study regarding the epidemiology and natural history of colorectal cancer; estimates of variables related to the effectiveness of screening, including test accuracy, compliance rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of cancer cases and cancer deaths prevented by screening; and the effect of varying key variables (sensitivity analyses).
Quantitative data synthesis	Measures of effect, method of combining results	Descriptive review. Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	Narrative and tabulated study description
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	Meta-analysis not performed

Author, publication year	Intervention	Study design	Participants /Setting	Effectiveness Data	Cost Data	Outcome	Results	Level of evidence Conclusions
Maciosek 2006	CRC screening with Annual FOBT Sigmoidoscopy every 5 years colonoscopy every 10 years	Cost effectiveness study	Average-risk people aged 50 years Perspective: societal setting: Third-party payer USA	Data obtained from a systematic search of clinical studies: three RCTs and one quasi-randomised trial for FOBT; four case-control studies for sigmoidoscopy; one observational study for colonoscopy	3% discount rate were used for both costs and benefits Price year 2000 US Dollar	Clinically preventable burden measured as life year saved (LYS) Cost per life-year saved (LYS)	***Clinically preventable burden (referred to an hypothetical birth cohort of 4 million offered with screening at recommended intervals)*** 338,000 life years saved ***Death prevented (referred to an hypothetical birth cohort of 4 million offered with screening at recommended intervals)*** 31,500 ***Death prevented (referred to the current cross-section of people aged 50 and older offered with screening at recommended intervals)*** 18,800 ***Cost-effectiveness ratios*** Annual FOBT: $13,300/LYS Sigmoidoscopy every 5 years: $18,900/LYS Colonoscopy every 10 years: $8800/LYS	Colorectal cancer screening continues to be a high-impact, cost-effective service in the group aged 50 and older.

This analysis is an updated of results reported by Vijian et al, 2001

Quality assessment: Effectiveness Data: systematic review was performed

Cost Data: Data from Medicare and Kaiser Permanente

Author, publication year	Intervention	Study design	Participants/ Setting	Effectiveness Data	Cost Data	Outcome	Results*	Level of evidence Conclusions
O'Leary 2004*	CRC Screening using different strategies vs. no screening Flexisigmoidoscopy (FS) every 10 years Annual and biennial FOBT Colonoscopy every 10 years	Cost effectiveness study	Cohort of asymptomatic, average-risk individuals aged 55–64 years who were moving through a defined series of states towards death. Perspective: government-funded health system Setting: secondary care Australia	The effectiveness data were obtained from studies dating from 1987 to 2001. The effectiveness data were derived from a review and synthesis of completed studies.	Medicare Benefits Schedule fee for the cost of the FOBT test, pathology examinations and medical attendance. The cost of the screening tests, colonoscopy, flexible sigmoidoscopy and cancer treatment were based on data from a published study. Price year 2001 Australian Dollars (A$)	Life-years saved (LYS).	***Incremental LYS per 10,000*** (screening versus the no screening) <u>Flexible sigmoidoscopy:</u>154 <u>Colonoscopy:</u> 213 <u>Biennial FOBT:</u> 42 <u>Annual FOBT:</u> 203 ***Costs*** No screening: Aus$3,530 Flexible sigmoidoscopy: Aus$6,120 Colonoscopy: Aus$7,640 biennial FOBT: Aus$8,880 annual FOBT: Aus$13,050 ***Cost per life-year saved*** Colonoscopy: A$19 285; FS every 10 years: A$16 801; annual FOBT: A$46 900%; biennial FOBT: A$41183%	Cost effectiveness study The incremental cost per life-year saved by flexible sigmoidoscopy screening was A$16 801 compared with no screening, which is considered cost-effective in terms of health interventions (a figure of A$50 000 per life-year saved is often considered an upper guide for determining the cost-effectiveness of health-care interventions in Australia). Colonoscopy screening was also cost-effective while both biennial and annual FOBT screening were less cost-effective. Thus, colonoscopy is still of acceptable cost-effectiveness, but annual FOBT is not.

* Data were retrieve from the original publication and from the NHS EED structured abstract available at the www.thecochranelibrary.com

Quality assessment: Markov model was developed in order to simulate the progression of a CRC patient cohort.

Effectiveness Data: Systematic Review of literature not performed. Study designs and other criteria for inclusion in the review, sources searched to identify primary studies, criteria used to ensure the validity of primary studies, methods used to judge relevance and validity, and for extracting data were not reported. Cost data: All the categories of cost relevant to the health service perspective adopted seem to have been included in the analysis. The indirect costs were not included in the analysis.

Author, publication year*	Intervention	Study design	Participants/ Setting	Effectiveness Data	Cost Data	Outcome	Results	Level of evidence Conclusions
Tappenden 2007 *	Five alternative screening strategies for CRC were compared with no screening: biennial faecal occult blood testing (FOBT) for individuals aged 50 to 69 years; biennial FOBT for individuals aged 60 to 69 years; once only flexible sigmoidoscopy (FS) for individuals aged 55 years; once only FISG for individuals aged 60 years; and once only FS for individuals aged 60, followed by biennial FOBT for individuals aged 61 to 70 years.	Cost-effectiveness analysis and cost-utility analysis	Hypothetical cohort of 100,000 individuals from the general population in England without polyps or cancer. Setting: secondary care UK Perspective: health care system	The clinical effectiveness data were derived from published studies (1961 and 2003). Whist it is apparent from the reporting that a number of UK sources had been used, the details of individual trials were not presented.	The resource data were obtained from the literature and expert opinion. The price data were obtained from the NHS Reference Costs, from published studies and from clinical expert opinion. The costs were discounted at an annual rate of 3.5%. Price year: 2003 UK pounds sterling	Life-years gained (LYG) The quality-adjusted life-years (QALYs).	***Incremental LYG per 100,000*** (screening versus the no screening) biennial FOBT at age 50 - 69 years 0.026 biennial FOBT at age 60 - 69 years 0.0126 FS once at age 55 years 0.0237 FS once at age 60 years 0.0197 FS once at age 60 years and biennial FOBT at age 61 - 70 years 0.0271 ***Incremental QALYs per 100,000*** (screening versus the no screening) biennial FOBT at age 50 - 69 years 0.0227 biennial FOBT at age 60 - 69 years 0.0104 FS once at age 55 years 0.027 FS once at age 60 years 0.0221 FS once at age 60 years and biennial FOBT at age 61 - 70 years 0.0282 ***Incremental cost per LYG per 100,000 (UK pounds)*** (screening versus no screening) biennial FOBT at age 50 - 69 years 2,576.72 Biennial FOBT at age 60 - 69 years. 1,950.29	Screening using faecal occult blood testing (FOBT) and/or flexible sigmoidoscopy (FS) is a potentially cost-effective strategy for the early detection of colorectal cancer (CRC).

Author, publication year*	Intervention	Study design	Participants/ Setting	Effectiveness Data	Cost Data	Outcome	Results	Level of evidence Conclusions
							Incremental cost per QALY per 100,000 (UK pounds) (screening versus no screening) <u>biennial FOBT at age 50 - 69 years</u> 2,949.64 <u>biennial FOBT at age 60 - 69 years</u> 2,364.99 FS once at age 55 years, FS once at age 60 years, and FS once at age 60 years followed by biennial FOBT at age 61 to 70 years were dominant.	

* Data were retrieve from the original publication and from the NHS EED structured abstract available at the www.thecochranelibrary.com

Quality assessment: Effectiveness Data: The authors combined data from published studies. No systematic search for data was reported, and whilst this is not uncommon in modelling papers it does mean that any evaluation of the validity of the effectiveness parameters is limited or impossible. Both LYG and QALYs are valid measures of benefit that permit comparisons with the benefits of other health care interventions. The estimation of benefits was modelled using a state transition model. Cost Data: The analysis of the costs was consistent with the perspective adopted in this study, although a more detailed breakdown of the costs would have been more informative.

Author, publication year*	Intervention	Study design	Participants/ Setting	Effectiveness Data	Cost Data	Outcome	Results	Level of evidence Conclusions
Whynes 2004 *	Biennial FOBT screening vs. no screening	Cost effective ness analysis	153,000 asymptomatic individuals who were aged from 45 to 74 years Setting: primary care, Nottingham (UK) Perspective not reported	The resource data were derived from studies published between 1991 and 1993. Effectiveness data gathered between 1981 and 2003. Source of effectiveness data: single prospective study (RCT)	The costing was undertaken prospectively on the same group of patients as that used in the effectiveness study. Price year: 2002 UK pounds sterling	*Incremental cost-effectiveness ratio (ICER)*	*ICER of the screening programme* 1,584 (95% CI: 717 - 8,612) pounds per life-year gained. (under conservative assumptions) *Cost of screening per cancer detected* 5290 pounds	The screening programme is cost-effective. The ICER for FOB screening in the Nottingham trial is lower than the equivalent ratio for the national breast cancer screening programme. The estimates place Nottingham FOB screening well up the league table of cost-effective interventions more generally.

* As we were not able to retrieve the original publication of this cost effectiveness analysis, data were obtained from the NHS EED structured abstract available at www.thecochranelibrary.com

Quality assessment: Effectiveness Data: The study was a randomised controlled trial that was conducted in 92 general practices in and around Nottingham, UK. The trial was not blinded. The duration of follow-up was more than 20 years. No loss to follow-up was reported. The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcomes used were the compliance rate, positive test rate, detection rate and survival rate. The patients in the two groups were not shown to have been comparable at analysis. Impact of false-positive results not estimated.

Cost Data: The indirect costs were not included. No statistical analysis of the costs was performed. One-way sensitivity analyses were assessed using Monte Carlo simulation. All the parameters were varied across the ranges of their confidence intervals (CIs).

Author, publication year*	Intervention	Study design	Participants /Setting	Effectiveness Data	Cost Data	Outcome	Results	Level of evidence Conclusions
Lejeune 2004 *	Biennial faecal occult blood test (FOBT) for the screening of colorectal cancer (CRC) vs. no screening	Cost-effectiveness analysis and cost-utility analysis	Hypothetical cohort of 100,000 asymptomatic individuals aged 50 to 74 years. Setting: primary care France Perspective: health care insurance system	The effectiveness data and most resource use data were derived from a synthesis of studies published between 1987 and 2001.	The costs came from difference sources (i.e. the clinical trial and other published studies). Discounting was relevant, given the long timeframe of the analysis (20 years) and an annual rate of 3% was applied. Price year 2002. Euros (EUR).	Estimated life-years gained (LYG) Incremental cost-effectiveness ratios (ICERs)	*Estimated LYG per 100,000* (screening over no screening) <u>time horizon of 20 years</u> 2,888 (3,891 if undiscounted) <u>time horizon of 10 years</u> 1,458 (1,712 if undiscounted) *Incremental cost-effectiveness ratios* (screening over no screening) <u>time horizon of 20 years</u> EUR 3,375 (2,492 if undiscounted) <u>time horizon of 10 years</u> EUR 4,705 (4,007 if undiscounted)	A biennial faecal occult blood test (FOBT) was a cost-effective screening strategy for colorectal cancer (CRC) in France for asymptomatic individuals aged 50 - 74 years over no screening. With a time horizon of 20-years a 17.7% mortality reduction and a discounted incremental cost-effectiveness ratio of 3357 Euro per life-year was observed.

* Data were retrieve from the original publication and from the NHS EED structured abstract available at www.thecochranelibrary.com

Quality assessment: A published Markov model was used to model the clinical and economic outcomes associated with biennial FOBT screening.

Effectiveness Data: It appears that the primary studies have been identified selectively, rather than through a systematic review of the literature. Most of the evidence came from a clinical trial carried out in Burgundy (France).

Cost Data: The analysis of the costs was consistent with the perspective adopted in the study. The source of the costs was unclear.

Author, publication year	Intervention	Study design	Setting	Outcome	Results	Level of evidence Conclusions
Berchi 2004	Automated reading immunological test (Magstream) guaiac stool test (Hemoccult).	Cost effectiveness analysis	France perspective: screening organiser, i.e. the Social Security Service	Costs and the effectiveness of 20 years of biennial CRC screening	***Cost (in euros/ targeted person)*** 10 years Magstream 230 Hemoccult 177 20 years Magstream 316 Hemoccult 234 ***Discounted cost (in euros/targeted person)*** 10 years Magstream195 Hemoccult 151 20 years Magstream 238 Hemoccult 179 ***Effectiveness (in life-years)*** 10 years Magstream 9.7960 Hemoccult 9.7901 20 years Magstream 16.7201 Hemoccult 16.7003 ***Incremental cost-effectiveness ratio (in euros/YLS) of Magstream test instead of Hemoccult test*** 10 years 8983 20 years 4141 ***Discounted incremental cost-effectiveness ratio (in euros/YLS) of Magstream test instead of Hemoccult test*** 10 years 7458 20 years 2980	The use of Magstream for 20 years of biennial screening costs 59 euros more than Hemoccult per target individual, and should lead to a mean increase in individual life expectancy of 0.0198 years (i.e. about one week), which corresponds to an incremental cost-effectiveness ratio of 2980 euros per years of life saved. These results suggest that using an immunological test could increase the effectiveness of CRC screening at a reasonable cost for society.

Quality assessment: transitional probabilistic model (Markov model); epidemiological and costs data were given by the evaluation of a screening program run in Calvados from 1991 to 1994;

1.12 Effectiveness of screening programmes in different age range populations (GUAIAC and immunochemical FOBT)

1.12.1 Summary document

Rita Banzi

CLINICAL QUESTION 17

Which is the best age range for offering screening by GUAIAC testing?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: GUAIAC test from age 50–74
C: GUAIAC test other age ranges
O: Colorectal mortality, overall mortality after at least 5 (10) years of follow up, colorectal cancer incidence, incidence of interval cancer
S: RCTs, systematic reviews of RCTs, cohort- and case-control studies

CLINICAL QUESTION 17B

Which is the best age range for offering screening by immunological/immunochemical testing?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Immunological/immunochemical test from age 50-74
C: Immunological/immunochemical test other age ranges
O: Colorectal mortality, overall mortality after at least 5 (10) years of follow up, colorectal cancer incidence, incidence of interval cancer
S: RCTs, systematic reviews of RCTs, cohort- and case-control studies

SEARCH METHOD

In order to retrieve relevant literature for question 17 we searched MedLine for publications in English, French, Italian, and Spanish using the following search strategy:

("Mass Screening" [MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms" [Mesh] OR "Colorectal Neoplasms" [Mesh] OR "Colonic Polyps" [Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*)

AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac)

We limited our search to Humans in specific age ranges (Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years).

We also searched the Cochrane Library using the following search strategy:
("Mass Screening" [MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms" [Mesh] OR "Colorectal Neoplasms" [Mesh] OR "Colonic Polyps" [Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac)

For question 17b we further specified the above mentioned search strategies adding the term "immunochemical".

We also contacted experts in the fields to retrieve papers relevant to these issues. Moreover, we hand-searched references quoted in the Cochrane Review "Screening for colorectal cancer using the faecal occult blood test, Hemoccult"(1).

RESULTS

We were not able to retrieve specific trials where screening programmes for detecting colorectal cancer and adenomas were investigated in populations with age ranges different from 45-75 year old. None of the RCTs investigating annual or biennial screening by GUAIAC-FOBT test for detecting colorectal cancer and adenomas reported a formal subgroup analysis regarding different efficacy of the screening in different age group. (2,3,4)

Data from the Nottingham trial at 11-years follow up showed no difference between the mortality rates for verified deaths from CRC between subjects older and younger than 60 year-old. (5).
However, the four trials included in the Cochrane review (1) included participants with different age range. Considering the limit of this indirect comparison, we reported the mortality reduction rates for the biennial screening in the four trials:

Study	Age range	RRR cancer mortality	Years follow up
Nottingham	45-75	13% (RR 0.87 CI95%0.78-0.97)	11 years
Funen	45-74	11% (RR 0.89 CI95% 0.78-1.01)	17 years
Minnesota	50-80	21% (RR 0.79 CI 95% 0.62-0.97)	18 years
Goteborg	60-64	16% (RR 0.84 CI95% 0.78-0.90)	15.5 years *

* Unpublished data: Hanglind 2005 personal communication

CONCLUSIONS

No information oneffectiveness are available which could indicate which is the best age range for offering screening for colorectal cancer and adenomas by GUAIAC and immunochemical FOBtesting.

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1.12.2 Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Hardcastle 2001 Nottingham	Biennial Hemoccult screening groups Control group: no screening	RCT	45–74 years 152,850 (76 466 FOB screening; 76 384 no screening)	CRC mortality reduction, CRC incidence, Number of CRC deaths, Death from all causes	11 years follow-up	*Mortality reduction* 15% reduction in cumulative CRC morality in screening group (OR=0.85, 95% CI 0.74-0.98; p=0.026) *Number of CRC cases* Screening group: 1.51 per 1000 person-years; Control group 1.53 per 1000 person-years; (OR=0.99, 95% CI 0.91-1.07; p=0.74) *Number of CRC deaths (verified)* Screening group: 0.60/1000person-years, Control group 0.70/1000 person-years; (OR=0.87, CI 0.78-0.97; p=0.01) *Deaths from all causes* Screening group: 24.18/1000person-years; Control group: 24.11/1000person-years; (OR=1.00, CI 0.98-1.02; p=0.79)	**II** After a median follow up of 11 years the results of the Nottingham trial showed a reduction in mortality from CRC in the intervention group of 15% while the number of cases of CRC in the control and intervention groups was similar.

Quality assessment: adequate randomisation procedure, adequate allocation concealment. Individual random allocation of subjects who lived in the Nottingham area (stratified by age, sex and place of residence). Blinding of the participants not applicable. Analysis by intention to screen. High rate of subjects completed at least one offered screening (60%). Blinded, standardised assessment of CRC mortality.

1.13 Efficacy and diagnostic accuracy of DNA testing

1.13.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 18

Is DNA stool testing offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: DNA Stool / Faecal DNA screening test
C: No screening
O: Colorectal cancer incidence, colorectal cancer mortality
S: (Systematic reviews of) RCTs, cohort- and case-control studies

CLINICAL QUESTION 18 B

Is stool DNA comparable to guaiac / immunochemical FOBT in its test performance characteristics (sensitivity and specificity)?

PICOS:

P: General population at average risk of colorectal cancer aged 50 years and older
I: Stool DNA
C: Guaiac / immunochemical FOBT
O: 1. Sensitivity / detection rate. 2. Specificity
S: (Systematic reviews of) diagnostic accuracy studies

SEARCH METHOD

Database searched: Medline, Embase, Cochrane Library

Search strategy for studies on prognosis

("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND ("DNA neoplasms"[Mesh] OR "DNA mutational analysis"[Mesh]) OR (DNA stool test) in Title, Abstract or Keywords

Search strategy for systematic review on diagnostic accuracy

("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND ("DNA neoplasms"[Mesh] OR "DNA mutational analysis"[Mesh]) OR (DNA stool test) AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*) AND systematic[sb]

Limits: Publication Date from 2000, Humans, English, French, Italian, Spanish

Search strategy for primary studies on diagnostic accuracy

("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND ("DNA neoplasms"[Mesh] OR "DNA mutational analysis"[Mesh]) OR (DNA stool test)

AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*)

Limits: Publication Date from 2000, Humans, English, French, Italian, Spanish

RESULTS

No systematic reviews or primary studies have been retrieved on the effectiveness of DNA testing in reducing colorectal cancer incidence or mortality.

We retrieved one systematic review published in 2006 (1), one systematic review published in 2008 (2) and one narrative review published in 2008 (3). All cited only one prospective study which assesses the diagnostic accuracy of DNA testing compared to Guaiac testing, the study published by Imperiale in 2004 which we considered in detail. We retrieved also three narrative reviews published in 2003 (5) and 2005 (6,7) but they were not analysed in detail because they included only 6 case control studies assessing the accuracy of DNA testing in subjects already known to have colorectal cancer, large premalignant adenomatous polyps or normal colon. These results were not further considered because results from case control studies with selected subjects are preliminary results aiming at assessing test performance under ideal conditions which usually overestimate diagnostic accuracy and they were surpassed by the results from the multicentre prospective study of Imperiale 2004 which assessed diagnostic accuracy of the test under real conditions found in clinical practice. One of these reviews (7) included also the study of Imperiale 2004. A cost effectiveness analysis of DNA stool test published in 2007 was retrieved and considered only for the results related to diagnostic accuracy (8). The review included the same case controls studies and Imperiale's study already included in the other review. Moreover it included the interim results of an ongoing study with similar design to the Imperiale study which assessed the diagnostic accuracy of a version1 stool DNA test. The preliminary results from a subset of 2,507 out of the 4,000 patients planned to be recruited showed a sensitivity for advanced neoplasia (CRC, high-grade dysplasia, villous component, or adenoma of size $\geq$1.0 cm) of 20% for the DNA test and of 13% for Hemoccult II. Finally the review reported the results of a phase I case control study assessing the accuracy of a new version of the test (version 2) on 40 subjects with CRC and 122 healthy control subjects: the sensitivity for CRC was 88% and the specificity was 82%.

Imperiale et al. 2004 (4) performed a multicentre prospective accuracy study comparing a version 1 stool DNA test vs. Guaiac (Hemoccult II) test on a subgroup of 2 507 subjects randomly selected out of 4 404 asymptomatic persons at average risk for colorectal cancer who completed the tests. The reference standard was colonoscopy for all subjects. The study was of good methodological quality.

The sensitivity of the faecal DNA panel was four times that of Hemoccult II for invasive cancer (51.6% vs. 12.9% P: 0.003) and more than twice as sensitive for adenomas containing high-grade dysplasia (32.5% vs. 15.0%). The sensitivity for any advanced neoplasia (defined as a tubular adenoma 1 cm in diameter or larger, a polyp with a villous histologic appearance, a polyp with high-grade dysplasia or cancer was 18.2% for DNA test and 10.8% for Guaiac (P<0.001).

This increase in sensitivity was achieved without a loss of specificity among persons with no polyps on colonoscopy (DNA testing: 94.4% Guaiac: 95.2%).

Itzkowitz 2008 (9) realized a phase Ia and a phase Ib case control study testing performance of a new version (version2) of stool DNA utilizing only two markers, hypermethylated *vimentin* gene (hV) and a two site DNA integrity assay (DY) on 40 subjects with CRC and 122 normal controls in the first study and on 42 subjects with CRC and 241 normal controls in the second study. Optimal cut off point based on the combined phase Ia and phase Ib dataset showed a sensitivity of 83% and a specificity of 82%. The authors concluded that this study provides validation of a simplified, improved sDNA test that incorporates only two Markers. The use of only two markers will make the test easier to perform, reduce the cost, and facilitate distribution to local laboratories. The present version of the assay appears to have potential for screening average risk individuals, if these results are confirmed in a screening population.

CONCLUSIONS

Only one prospective study comparing version 1 stool DNA with Hemoccult II in the general population at average risk of colorectal cancer has been published so far. A second similar study is underway. A phase I case control study has been conducted to test the performance of version2 stool DNA test. The results seems promising but the search is still in a very early stage and needs to be confirmed by large multicentre prospective trials on average risk population (LEVEL OF EVIDENCE III).

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1.13.2 Evidence tables

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Whitlock 2008	To assess the accuracy and potential harms of newer colorectal cancer screening tests (high-sensitivity FOBTs, faecal immunochemical tests, faecal DNA testing, and CT colonography) Reference standard: colonoscopy	Systematic review of SRs PubMed; DARE; CDSR; Institute of Medicine, National Institute for Health and Clinical Effectiveness, and Health Technology Assessment databases for recent systematic reviews (1999 –2006) MEDLINE and Cochrane January 2006 through January 2008 to locate additional studies published after the end date of the searches.	DNA testing: 1 study (Imperiale 2004) on 4404 average risk persons already considered by our review Immunochemical test: 9 study on 86498 average risk persons CT colonography: 7 studies located, 4 included on 4312 average-risk patients	Sensitivity specificity	**Immunochemical tests** had higher sensitivity for colorectal cancer (61% to 91%) than was reported for non rehydrated Hemoccult II (25% to 38%). Estimated specificity varied across faecal immunochemical tests (91% to 98%), and, in most studies, specificity appears lower than the reported specificity of non rehydrated Hemoccult II (98% to 99%) **DNA testing:** Onetime faecal DNA testing was more sensitive for adenocarcinoma than was Hemoccult II (sensitivities of 51% [CI, 34.8% to 68.0%] and 12.9% [CI, 5.1% to 28.9%], respectively). Both faecal DNA testing and Hemoccult II had poor sensitivity for advanced carcinoma. **CT colonography** Results from the two larger and high quality studies (Pickhardt 2003, Johnson 2008) Sensitivity Adenoma ≥ 10 mm 93.8 (82.8–98.7) 90 (84–96) Adenoma ≥ 6 mm 88.7 (82.9–93.1) 78, (71–85) Specificity Lesion ≥ 10 mm 96.0 (94.8–97.1) 86 (81.3–90.0) Lesion ≥ 6 mm 79.6 (77.0–82.0) 88 (84.0–92.0)	**III** **Immunochemical tests** had superior single test sensitivity for colorectal cancer and possibly for advanced neoplasia compared with Hemoccult II. Faecal immunochemical tests had similar or somewhat lower specificity, **DNA testing:** showed improved sensitivity for colorectal cancer but not adenomas, similar or slightly reduced specificity, and higher positive rates compared with Hemoccult II. This study's findings may not be generalisable to population screening because participants were relatively older (three quarters were _65 years of age, compared with screening beginning at age 50 years) and the version of PreGen Plus tested has been supplanted by other versions for which there are no screening population studies. **CT colonography** screening by trained and experienced radiologists had sensitivity similar to that of colonoscopy for colorectal cancer and large adenomas (≥10 mm).

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
					Sensitivity and specificity estimates from 2 smaller fair quality studies comparing CT colonography with colonoscopy are less informative because these studies detected relatively few lesions and their primary purposes were 1) to examine the relative accuracy of 2-dimensional vs. 3-dimensional methods for displaying and reviewing CT colonography images and 2) to compare radiologist performance. Thus, these studies do not provide overall results for the population but rather report subsets of data to compare readers or technologies. Results are generally consistent, with better sensitivity for larger (compared with smaller) lesions, no clear differences between 2- and 3-dimensional approaches	However, estimates of sensitivity of CT colonography for smaller adenomas (≥6 mm) was more variable between studies. Other uncertainties may affect considerations of whether this test is ready for widespread population screening. These include questions about potential harms from radiation exposure, uncertainty about extracolonic findings, uncertainty about test referral thresholds and repeat test intervals, and judgments about how the test performance seen in clinical studies will translate to the conduct of CT colonography screening examinations in community settings.

Quality assessment: more than one database searched. Publication bias: not specified if only English language studies considered. Selection of studies, data abstraction done by two independent reviewers. Quality assessment of primary studies done. Trial flow reported Characteristic of included studies reported.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Imperiale 2004	Faecal DNA version 1 vs. Guaiac (Hemoccult II) FOBT Reference standard: colonoscopy	Cross-sectional diagnostic accuracy study USA	A subgroup of 2507 subjects was analysed randomly selected out of 4404 asymptomatic persons at average risk for colorectal cancer who completed the tests	Sensitivity specificity	**Invasive adenocarcinoma** Sensitivity DNA testing: 51.6% Guaiac: 12.9% (P: 0.003) **Carcinoma in situ** Sensitivity DNA testing: 40.8% Guaiac: 14.1% (P<0.001) **Adenoma with high degree dysplasia** Sensitivity DNA testing: 32.5% Guaiac: 15.0% **Advanced neoplasia (defined as a tubular adenoma 1 cm in diameter or larger, a polyp with a villous histologic appearance, a polyp with high-grade dysplasia, or cancer** Sensitivity DNA testing: 18.2% Guaiac: 10.8% (P<0.001) Specificity DNA testing: 94.4% Guaiac: 95.2%	**III** The sensitivity of the faecal DNA panel was four times that of Hemoccult II for invasive cancer and more than twice as sensitive for adenomas containing high-grade dysplasia. This increase in sensitivity was achieved without a loss of specificity among persons with no polyps on colonoscopy. Although this study was not powered to compare the tests among the different stages of cancer, the faecal DNA panel appears to be more sensitive than Hemoccult II for the detection of early (TNM stage I or II) colorectal cancer. However, since this result was not prespecified in the analytic plan, it should be considered preliminary.

Quality assessment: prospective cohort study. Spectrum of patients representative of the patients who will receive the test in practice. Selection criteria clearly described. Index test and reference test results interpreted without knowledge of the results of the other test. Execution of index test, comparator and reference standard clearly described. The entire selected sample received reference standard (avoidance of selection bias)

Author, publication year	Study objective Screening test evaluated Comparator test	Study design	Included studies	Outcome	Results	Level of evidence Conclusions
Zauber 2007	To perform a cost effectiveness analysis of DNA stool test Only results about diagnostic accuracy were considered	Systematic review Medline, up to January 2007, Technology Evaluation Center (TEC) report 2006	3 studies: Imperiale 2004 version 1 sDNA tested on 4404 average risk persons already considered by our review in detail. One abstract by a prospective study with similar design to Imperiale's study underway by Ahlquist 2007 which planned to accrue 4000 patients by 2006. Version 1 sDNA tested. Interim results among 2507 patients Itzkowitz 2007: version 2 sDNA tested in phase I case control study on 40 patients with CRC and 122 controls health subjects	Sensitivity specificity	Imperiale 2004: Onetime faecal DNA testing was more sensitive for adenocarcinoma than was Hemoccult II (sensitivities of 51% [CI, 34.8% to 68.0%] and 12.9% [CI, 5.1% to 28.9%], respectively). Both faecal DNA testing and Hemoccult II had poor sensitivity for advanced carcinoma. Interim results of Ahlquist 2007 Sensitivity for advanced neoplasia (CRC, high-grade dysplasia, villous component, or adenoma of size $\geq$1.0 cm): DNA test: 20% Hemoccult II: 13% Itzkowitz 2007 Sensitivity: CRC 88% Specificity: 82%	III

Quality assessment: more than one database searched. Publication bias: not specified if only English language studies considered. Selection of studies, data abstraction done by two independent reviewers: not specified. Quality assessment of primary studies not done. Trial flow not reported Characteristic of included studies reported.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Itzkowitz 2008	Faecal DNA version 2 Reference standard: colonoscopy The same markers used in the phase 1a study were analysed using the identical sample collection kit, DNA stabilisation buffer, and gel-based DNA purification	Cross-sectional diagnostic accuracy study. The same centres which participated in phase Ia study USA	42 subjects with CRC diagnosed at colonoscopy 241 normal subjects at colonoscopy	Sensitivity specificity	Phase Ib Sensitivity : 86% [72.2–93.3%] Specificity: 73% [67.1–78.2%] Phase Ia Sensitivity : 88% [73.9–94.5%] Specificity: 82% [74.2–87.8%] Optimal cut off point based on the combined phase Ia and phase Ib dataset Sensitivity : 83% [73.4–89.5%] Specificity: 82% [77.2–85.2%]	**III** This study provides validation of a simplified, improved sDNA test that incorporates only two markers. The use of only two markers will make the test easier to perform, reduce the cost, and facilitate distribution to local laboratories. The present version of the assay appears to have potential for screening average risk individuals, if these results are confirmed in a screening population.

Quality assessment: case control study: patients with invasive CRC and normal controls. Selection criteria clearly described. Index test performed after knowing the results of the reference standard. Execution of index test, comparator and reference standard clearly described. The entire selected sample received reference standard (avoidance of selection bias)

1.14 Adverse events of FOBT, sigmoidoscopy, colonoscopy

1.14.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 19

What is the rate of negative side effects of guaiac FOBT screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: FOBT
C: Not applicable
O: False-positive tests, false-negative tests, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCTs, pilot studies

CLINICAL QUESTION 20

What is the rate of negative side effects of immunological FOBT screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Immunological / immunochemical FOBT
C: Not applicable
O: False-positive tests, false-negative tests, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCTs, pilot studies

CLINICAL QUESTION 21

What is the rate of negative side effects of flexible sigmoidoscopy screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Flexible sigmoidoscopy
C: Not applicable
O: False-positive tests, false-negative tests, rates of perforations, bleeding and other serious adverse effects, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCTs, pilot studies

CLINICAL QUESTION 22

What is the rate of negative side effects of colonoscopy screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Colonoscopy
C: Not applicable
O: False-positive tests, false-negative tests, rates of perforations, bleeding and other serious adverse effects
S: (Systematic reviews of) RCTs, pilot studies

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic.

For questions 19 and 20 we also searched MedLine for publications in English, French, Italian, and Spanish using the following search strategy:

("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac)

We limited our search to Humans in specific age ranges (Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years).

We also searched the Cochrane Library using the following search strategy:

("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac)

For questions 21 and 22 we searched MedLine using the following search strategy:
exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy OR sigmoidoscopy). The search was limited to paper published in English, French, and Italian between 2007 and 2008.

RESULTS:

We found 13 studies relevant for these questions. Four assessed the outcomes for sigmoidoscopy (1, 2,4,5,11), three for colonoscopy (6,7,9,12,13), one compared the outcomes between FOBT and sigmoidoscopy (8), and one compared the outcomes between FOBT, colonoscopy and sigmoidoscopy (3). One is a pilot study of screening by FOBT on the general population in the UK (10). For false positive and positive rate of FOBT we also considered the four published randomised controlled trials included in the Cochrane Systematic Review.

For information from randomised controlled trials of colorectal cancer screening using FOBt, see Chapter 3.

Complications of colonoscopy

	Lieberman 2000 (7)	Regula 2006 (9)	Schoenfeld 2005 (6)	Segnan 2005 (SCORE 2) (8)	Segnan 2007 (SCORE 3) (3	UK CRC screening pilot 2004 (10)	UK FS screening trial Investigators 2002 (2)	Rainis 2007 (12)	Kim 2007 (13)
Severe complications	0.3%	0.1%	0%	0.3%:	Not reported	0.05%	0.5%	0.08%	0%
Minor complications	Not reported	Not reported	Not reported	3.9%	Not reported	0.56%	0.4%		

Complications of sigmoidoscopy

	Segnan 2002 (SCORE) (4)	Segnan 2005 (SCORE 2) (8)	Segnan 2007 (SCORE 3) (3	Weissfeld 2005 PLCO (1)	UK FS screening trial Investigators 2002 (2)	NORCCAP study 2003 (5)	Knox 2007 (11)
Severe complications	0.02%	0.02%	Not reported	Not reported	0.03%	Not reported	0%
Minor complications	0.6%	0.5%	Not reported	Not reported	0.2%	Not reported	0%

Adverse events of FOBT (Guaiac and immunochemical)

	Segnan 2005 (SCORE 2) (8)	Segnan 2007 (SCORE 3) (3)	UK CRC screening pilot (10)	Nottingham trial	Funen trial	Goteborg trial	Minnesota trial	NORCCAP study 2003 (5)
FP rate	CRC or advanced adenoma: 54%	CRC or advanced adenoma: 71.6%	CRC:89.1% Adenoma: 65%	CRC: 82.9%-90.1% Adenoma: 45.5%-57.2%	CRC: 81.3%-94.8% Adenoma: 61.7%-85.4%	No data	CRC: 93.9%-99.1% Adenoma: 89%-94%	CRC or advanced adenoma: 74%
FN rate	No data	No data	No data	No data	No data	No data	No data	No data

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1.14.2 Evidence tables

NOTE: For the other evidence tables corresponding to question 19, 20, 21 and 22, see chapter 3.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Knox 2007	Modified colon endoscopy (MCE) and flexible sigmoidoscopy (FS)	Retrospective chart review	MCE: 48 patients FS: 35 patients patients in the MCE group were statistically significant older than those in the FS group. Recruitment between 2003 and 2005 family medicine practices Los Angeles USA	Completion rates, number of complications, depth reached, anatomic site visualized, and information about the number and nature of clinical findings	**Completion rates** MCE: 83.3% FS: 75% No difference Statistically significant differences were found in the anatomic site visualized (P <.01) and depth reached (P <.01). **Clinical pathologies** MCE: 58% of patients FS: 37% of patients No complications (bleeding, infection, perforation, and other) were reported in either group	**IV** This study suggest that MCE can be an acceptable alternative to FS in office settings for colorectal cancer screening. No complications (bleeding, infection, perforation, and other) were reported in either group.

Quality assessment: baseline characteristics were not homogenous; retrospective design; outcome assessment was not blinded to group treatment.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Rainis 2007	Colonoscopy	Retrospective chart review	10,866 Colonoscopies 55% were women 84% persons were 50 years old or over Between January 2001 and September 2003	Indication for endoscopy, endoscopic and histopathologic findings, complications	**Indication for endoscopy** Family history of CRC: 2352 (22%) Rectal bleeding 1879 (17%) Abdominal pain 1503 (14%) Anemia 1050 (10%) Occult blood 1124 (10%) Change of bowel habits 562 (5%) Others 2406 (22%) **Pathologic findings** 3533 in 2978 colonoscopies **Colonoscopy completed successfully to the cecum** 93% of patients **serious complications** 0.08% during or immediately after colonoscopy (one gastrointestinal bleeding that required hospitalisation, 8 perforations of the colon that required surgical intervention)	**IV** This study suggests that open access colonoscopy is a reliable and safe method for screening average risk population.

Quality assessment: N/A

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Kim 2007	Colonoscopy	Cohort study	4,629 adults underwent colonoscopic screening January 2003 to September 2005 Korea	Colonoscopic and pathologic findings	**Complete colonic evaluation** 4,491 (97.0%) **Adenomatous polyps** 804 (17.9%) **Advanced adenomas** 153 (3.4%) No significant complications such as bowel perforation or massive bleeding requiring transfusion in relation to the procedure.	**III** Colonoscopy performed by experienced colonoscopists as a screening test is feasible for detecting subjects with colorectal polyps

Data extracted from the abstract as the full text was not available.

Quality assessment: N/A

1.15 Effectiveness of screening programmes with immunochemical FOBT

1.15.1 Summary document

Rita Banzi

CLINICAL QUESTION 23

Is immunochemical FOBT screening offered to the general population age 50 and older effective in reducing colorectal cancer mortality?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: I-FOBT screening
C: No screening
O: Colorectal cancer mortality; incidence
S: (Systematic reviews of) RCT, cohort- and case-control studies

SEARCH METHOD

In order to retrieve relevant literature we searched <u>MedLine</u> for publication in English, French, Italian, and Spanish using the following search strategy:

("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac) AND immunochemical

We limited our search to Humans in specific age range (Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years).

We also searched the <u>Cochrane Library</u> using the following search strategy:

("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac) AND immunochemical.

Finally the experts suggested further literature relevant for this issue.

RESULTS

A cluster randomised controlled trial was performed on individuals aged 30 years or more recruited into the screening program in the Chinese county of Jiashan. (1) The primary screening methods included immunochemical faecal occult blood testing (RPHA-FOBT) and quantitative individual risk assessment of colorectal cancer. The cumulative incidence of both colon and rectal cancer was almost identical in the screened (208 per 100 000; 95% CI, 196– 218) and control group (244 per 100 000; 95% CI, 233–255).

We also retrieved three Japanese case control studies (2-4) relevant for this issue. The first study published in 1995 evaluated the efficacy of I-FOBT in study areas where no previous and no other concomitant colorectal cancer screening had been performed. (2) Case series in the study were 193 cases that died of colorectal cancer. Odds ratios (OR) of dying of colorectal cancer for those screened within 1 to 5 years of case diagnosis vs. those not screened were reduced by 23%-60%, with a significant reduction for those screened within 1, 2, and 3 years before diagnosis (0.40 [95% confidence interval (CI) 0.17-0.92], 0.41 (95% CI 0.20-0.82), and 0.48 (95% CI 0.25-0.92), respectively). Another case control study evaluated FOBT screening in a town where the Hemoccult test was performed during the early years and subsequently an I-FOBT was introduced(3). Cases consisted of 51 subjects with fatal colorectal cancer and controls were selected from the list of residents who were alive at the time of diagnosis of the corresponding case and had been living in the town, matched by gender and by age. The OR of dying of colorectal cancer was calculated to be 0.19 (95% CI: 0.05-0.70) for those screened with the I-FOBT alone during the preceding 1 year after adjustment for previous screening histories with the Hemoccult test. More recently, Nakajima et al.conducted a study on 357 consecutive patients enrolled in the areas where an annual screening programme with immunochemical FOBT has been offered to all inhabitants aged 40 years or over(4). The OR for those screened within 3 years before the diagnosis vs. those not screened was 0.54 (95% confidence interval (CI) 0.29–0.99).

Finally a recent Italian screening programme by biennial immunochemical FOBT reported a retrospective comparison of cancer rate and stages between average risk screening participants and those who did not participate in the screening programme. (5) Although the overall cancer rate was similar in the two populations (1.23 versus 1.20 per 1000 person-years), there were significant differences in TNM stage distribution between the two groups (stage III–IV cancers 0.24 versus 0.74 per 1000 respectively, p = 0.009).

CONCLUSIONS

One RCT and three case-control studies reported that a screening programme with immunochemical FOBT can be effective for prevention of advanced colorectal cancer. Efficacy of the screening would be higher for the I-FOBT than for Hemoccult test but a head to head comparison of the two techniques is not available. (LEVEL OF EVIDENCE II-IV)

A large cross-sectional study reported that colorectal cancers detected by immunochemical FOBT screening are identified at an earlier pathological stage, with significant prognostic and economic advantages to the populations screened. (LEVEL OF EVIDENCE V)

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1.15.2 Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Zheng 2003	Experimental intervention: Immunochemical FOBT (RPHA-FOBT) one round. Individuals with a positive FOBT were asked to undergo sigmoidoscopy. If FS failed to detect colorectal lesions, the participants were asked to repeat the FOBT. Those without a lesion found by FS but with a positive repeated FOBT were re-examined by 150-cm colonoscopy to confirm the results. Control intervention: no screening	Cluster randomised, controlled, population-based trial	Screening group: 10 townships with a total of 94,423 residents Control group: 11 townships with 97,838 residents individuals aged 30 years or more in the screening group were recruited into the screening program response rate: 80.3% From May 1989 to May 1990. Jiashan County China	Colon cancer mortality Rectal cancer mortality	7 years	**Age adjusted and gender adjusted CRC incidence** Screening group: 17.6 per 100,000 (95% CI, not reported) Control group: 17.9 per 100,000 (95% CI, not reported) **Overall Mortality** Screening group: 7.6 per 100,000 (95% CI, not reported) Control group: 7.1 per 100,000 (95% CI, not reported) p>0.05 **Cumulative colon cancer mortality** Screening group: 90 per 100,000 (95% CI, 83–97) Control group: 83 per 100,000 (95% CI, 76–90) p=0.222 **Cumulative rectal cancer mortality** Screening group: 110 per 100,000 (95% CI, confidence interval, 102) Control group: 161 per 100,000 (95% CI, 152–170) p=0.003	**II** Mass screening with a reverse passive I-FOBT test along with an individual attributive degree value score was effective in reducing mortality from rectal cancer but not in reducing mortality from colon cancer or the incidence of colorectal cancer.

Quality assessment: sequence generation using random digits; allocation concealment not clear; unit of allocation: townships, unit of analysis: individuals no inter-cluster correction; blinded assessment of outcome (technicians reading the FOBT results were independent of the field interviewers and the evaluators).

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Saito1995	Immunochemical FOBT	Case-control study	Cases: 193 subjects who died of colorectal cancer. Controls: three controls were selected randomly from the list of individuals who were alive at the time of diagnosis of the corresponding case and had been living in the same area as the case 40 year old and older Japan	Odds ratios of dying of colorectal cancer	***OR for those screened within 1 to 5 years of case diagnosis vs. those not screened*** 1 yr: 0.40 [95% confidence interval (CI) 0.17-0.92], 2 yrs: 0.41 (95% CI 0.20-0.82), 3 yrs: 0.48 (95% CI 0.25-0.92) 4 yrs: 0.69 (95% CI 0.34-1.39) 5 yrs: 0.77 (95% CI 0.34-1.74)	IV These results suggest that colorectal cancer screening by the immunochemical faecal occult blood test would reduce mortality from colorectal cancer.

Quality assessment: adequate definition of case and selection of controls; matching by gender and by age; ascertainment of exposure through screening history and staff was blind to subject's status (case or control).

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Nakajima 2003	Immunochemical FOBT	Case-control study	Cases: 357 consecutive patients in the study areas clinically diagnosed as having advanced colorectal cancer or a tumour invading the muscularis propria or deeper, that is, T2–T4 in TNM classification Controls: three controls were selected for each case inhabitants aged 40 years or over Japan	Odds ratios of dying of colorectal cancer	***OR for those screened within 3 years of case diagnosis vs. those not screened*** 0.54 (95% confidence interval (CI) 0.29–0.99). The ORs were lower for rectum than for colon (0.32–0.73 and 0.84–1.18 for rectum and colon, respectively).	IV These results suggest that colorectal cancer screening by the immunochemical faecal occult blood test would reduce mortality from colorectal cancer.

Quality assessment: adequate selection of cases and representativeness; matched by gender, age, residential area and exposure status to screening within 1 year before case diagnosis. Ascertainment of exposure using medical records.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Parente 2009	Biennial Immunochemical FOBT (1-day) Colonoscopy offered to those with a positive result	Cross-sectional study Colorectal cancer screening programme in a population at average risk	78083 asymptomatic subjects involved in CRC screening programme, aged 50-69 were invited Men = 18 314 Women = 20 379 Lecco, Italy	Uptake Compliance to colonoscopy Detection rate for 1000 FOBT (DR) and positive predictive value (PPV)* for cancer and adenoma Tumour stages according to screening status (historical comparison with no screened cohort)	*Uptake* 38693 (49.6%) actually screened *FOBT positive result* 2392 (6.2%) *Number of colonoscopies* 2052 (92.0% of eligible subjects) *Colorectal cancer* Prevalence: 95 (4.6%) DR: 2.5% (95% CI 2.0 to 3.0) PPV: 4.0% (95% CI 2.1 to 5.4) *Advanced adenoma prevalence* Prevalence: 673 (32.7%) DR: 17.4% (95% CI 16.1 to 18.8) PPV: 28.1% (95% CI 26.3 to 29.9) *Any adenoma* Prevalence: 876 (42.7%) DR: 22.6% (95% CI 21.2 to 24.2) PPV: 36.6% (95% CI 34.7 to 38.6) *Overall cancer rate (per 1000 person-years)* screened cohort: 1.23 non screened cohort: 1.20 *Rate of stage III–IV cancers(per 1000 person-years)* screened cohort: 0.24 non screened cohort: 0.74 p = 0.009	**V**: cross-sectional These data are encouraging in terms of compliance with faecal testing and colonoscopy, as well as the detection rate of neoplasia. Colorectal cancers detected by immunochemical FOBT screening are identified at an earlier pathological stage, with significant prognostic and economic advantages to the populations screened.

*based on all FOBTs, not only on patients eligible for colonoscopy.

Quality assessment: Not applicable.

1.16 Additional evidence tables prepared after December 2009

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Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Atkin W.S., 2010	To examine the hypothesis that only one flexible sigmoidoscopy screen undertaken between ages 55 and 64 years is a cost-effective and acceptable method to reduce colorectal cancer incidence and mortality. Multicenter randomised controlled trial UK	170,432 men and women aged 55-64 years from 14 UK centres , who had indicated on a previous questionnaire that they would accept an invitation for screening, were randomly allocated to the intervention group (offered flexible sigmoidoscopy screening) or the control group (not contacted). No difference between the two groups for age and gender.	Invitation for a flexible sigmoidoscopy screening: Intervention group (I): Patients were offered an appointment for a flexible sigmoidoscopy screening (n=57237) or Control group (C): patients were not contacted (n=113195)	Incidence and mortality of colorectal cancerr	Median follow-up=11.2 years Intervention group=57099 Not screened=16478 Screened= 40621 Control group=112939 Tot=170038 **Cases of colorectal cancer** I vs C = 706 vs 1818 **Death for colorectal cancer** I vs C = 189 vs 538 **Incidence** All sites, hazard ratio (95%CI) I vs C = 0.77 (0.70-0.84) p<0.0001 Screened vs C= 0.67 (0.60-0.76) **Mortality for colorectal cancer, hazard ratio (95%CI)** I vs C = 0.69 (0.59-0.82) p<0.0001 Screened vs C= 0.57 (0.45-0.72) **Numbers needed to be screened to prevent** Colorectal cancer diagnosis= 191 (95% CI: 145–277) Colorectal cancer death= 489(95% CI: 343–852)	**II** Incidence of and mortality from colorectal cancer are significantly reduced in people undergoing a single flexible sigmoidoscopy examination between 55 and 64 years of age. After 11 years of follow-up, colorectal cancer incidence was reduced by a third and colorectal cancer mortality by more than 40% in those who underwent screening. Flexible sigmoidoscopy is a safe and practical test and, when offered only once between ages 55 and 64 years, confers a substantial and longlasting benefit

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; 256 patients from control group and 138 from intervention group were excluded the analysis.

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Brenner 2010	To examine whether receiving a colonoscopy in the preceding 10-year period, compared with no colonoscopy, was associated with prevalence of advanced colorectal neoplasms (defined as cancers or advanced adenomas) at various anatomical sites. Cross-sectional survey	3,287 participant in a screening colonoscopy trial in German 55 years or older Participants were asked if they ever had had a previous colonoscopy for any reason by a structured questionnaire before the examination,	Prevalence of advanced neoplasia among participants who had had a previous colonoscopy in the 10-year period before the screening colonoscopy examination with participants who had not had a previous colonoscopy.	2,701 had not no previous colonoscopy (ie, group 1) and 586 had a previous colonoscopy 1 – 10 years before the screening colonoscopy prevalence of advanced neoplasia no colonoscopy: 11.4% colonscopy: 6.1% adjusted prevalence ratio (for age, sex, and family history of colorectal cancer): PR: 0.52, 95%CI = 0.37 to 0.73). Adjusted prevalence ratio for right-sided colon 1.05 (95% CI = 0.63 to 1.76) Adjusted prevalence ratio for left-sided combined were and colon and rectum 0.33 (95% CI = 0.21 to 0.53).	**V** Colonoscopy provides strong protection against advanced neoplasms in the left colon and rectum, even in the community setting. Despite the lack of data from randomised trials, screening for colorectal cancer by endoscopy of the large bowel is among the most powerful measures for reducing the cancer burden in Western societies.

Author, publication year	Study Objective Study Design	Characteristic of participants	Index test Reference standard	Outcome	Results	Conclusion Level of evidence
Eliakim 2009	To examine to assess the diagnostic accuracy of the second generation Pill Camm colon capsule endoscopy Cross-sectional diagnostic accuracy study	98 (18–57 years of age) patients who were scheduled to undergo colonoscopy for either known or suspected colonic disease were enrolled in the study. Indications included colorectal cancer screening, personal history of colorectal cancer or adenomatous polyps and at least 5 years since last conventional colonoscopy, clinical symptoms such as rectal bleeding, positive faecal occult blood test, recent change of bowel habits, or positive findings in the colon on gastrointestinal imaging,	Index test: Pill Camm capsule endoscopy Reference standard: colonoscopy	Sensitivity and specificity for polyp detection.	Polyps ≥ 6 mm: sensitivity : 89 (70– 97) specificity: 76 (72 – 78) Polyps: ≥ 10mm: Sensitivity: 88 (56 – 98) Specificity: 89 (86 – 90)	**III** This first feasibility study of the second-generation PillCam Colon 2 capsule endoscopy system compared with conventional colonoscopy suggests that the new system has the potential for improved sensitivity of colon capsule endoscopy comparedwith the first-generation system. Indeed, the sensitivity of 89% for detection of patients with polyps ≥ 6mmobtained in this study is very encouraging

Quality assessment: prospective recruitment; spectrum of patients representative of the individuals who will receive the test in practice; patients selection criteria clearly described; verification by reference standard of all subjects; execution of the index and comparator tests adequately described; execution of the reference standard described; independent and blind interpretation of index test and reference standard results: yes for index test, not clear for reference standard; no withdrawal from the study.

Author, publication year	Study Objective Study Design	Characteristic of participants	Index test Reference standard	Outcome	Results	Conclusion Level of evidence
Gay 2009	To evaluate the ability of Colonic Capsule Endoscopy to detect clinically relevant colonic findings as compared with colonoscopy, and further, to test the assumption that CCE used in the frame of colorectal cancer (CRC) screening could accurately discriminate patients deserving a complete colonoscopy. Cross-sectional diagnostic accuracy study	128 (55 ± 14) patients with an indication for colonoscopy: Indications for colonoscopy were defined by a known personal history of CRC and / or colonic polyps and no colonoscopy performed during the previous 3 years; a familial history of CRC and / or colonic polyps and no colonoscopy performed during the previous 3 years for patients over 50 years of age; any colonic positive finding on another imaging modality; a history of ulcerative colitis; a positive FOBT within the previous 3 months; or any of the following symptoms: rectal bleeding, hematochezia, melena, or a recent change in bowel habits.	Index test: Pill Camm capsule endoscopy Reference standard: colonoscopy	Sensitivity and specificity for any positive finding that would justify a colonoscopy.: presence of one or more polyps ≥ 6 mm in diameter; presence of three or more polyps ≤ 6 mm in diameter; and detection of any significant mucosal lesion such as cancer, inflammatory changes suggesting inflammatory bowel disease, and so on. The accuracy of the CCE to select patients who deserve a colonoscopy was assessed by calculating the PPV and NPV ofthe CCE.	Colonic findings sensitivity : 87.5% (confidence interval (CI) 79.4 – 95.6% specificity: 75.8 % (CI 65.4 – 86.2 %). PPV: 78.9% (95% CI 71.7– 87.9%) NPV: 85.4 % (95 % CI 79.2 – 91.6 %),	**III** In the setting of this study, CCE seemed to be effective in detecting clinically significant colonic findings in patients with an indication of colonoscopy. The high NPV and excellent tolerance of CCE suggest that it could be evaluated in large CRC-screening programs and further studies in screening conditions should also evaluate its cost – efficacy ratio

Quality assessment: prospective recruitment; spectrum of patients representative of the individuals who will receive the test in practice; patients selection criteria clearly described; verification by reference standard of all subjects; execution of the index and comparator tests adequately described; execution of the reference standard described; independent and blind interpretation of index test and reference standard results: yes for index test and reference standard; no withdrawal from the study.

Author, publication year	Study Objective Study design	Study Participants	Inter-vention	Out-comes	Results	Conclusion
Ladabaum U., 2001	To examine the potential cost-effectiveness of aspirin chemoprophylaxis in relation to screening. Cost-effectiveness analysis USA	General U.S. population; 50 to 80 years of age.	Aspirin therapy in patients screened with sigmoido-scopy every 5 years and faecal occult blood testing every year (FS/FOBT) or colonoscopy every 10 years (COLO).	Dis-counted cost per life-year gained, cost-effective ness ratio	ASA=aspirin **Mean discounted life-years per person** <u>All person screened</u> FS/FOBT=18773 FS/FOBT/ASA=18771 COLO=18768 COLO/ASA=18769 <u>25% of person screened, 75% not screened</u> FS/FOBT=18721 FS/FOBT/ASA=18734 COLO=18719 COLO/ASA=18734 <u>No person screened</u> Natural history=18703 ASA=18722 **Cost effectiveness ratio, $ per life-year** COLO/ASA vs COLO = 149161 FS/FOBT/ASA less effective and more costly than FS/FOBT FS/FOBT/ASA vs ASA =26315 COLO/ASA vs ASA =30822 ASA is more effective and less costly than no aspirin or screening FS/FOBT vs no aspirin or screening=16844 COLO vs no aspirin or screening=20172	The model suggests that the addition of aspirintherapy in a population adhering to screening is not likely to be beneficial for colorectal cancer prevention. Aspirin use should be based on other clinical considerations. While aspirin alone may be of some benefit in colorectal cancer prevention, it cannot substitute for screening. As suggested by the results and many previous investigations, screening is highly cost-effective and remained so in our model for patients already taking aspirin, even when aspirin was assumed to confer a high degree of colorectal cancer chemoprevention.

Quality assessment: The Markov model estimated the clinical and economic consequences of six strategies: natural history (no aspirin or screening), FS/FOBT, COLO, aspirin alone (ASA), FS/FOBT and aspirin (FS/ FOBT/ASA), and colonoscopy and aspirin (COLO/ ASA).

Effectiveness Data: Systematic Review of literature: Medline (1980-1999).

Cost data: Procedure costs were derived from Medicare fee schedules and include professional fees and median procedure reimbursement. Complication costs were derived from relevant diagnostic related groups. Costs for care of stage-specific colon cancer were taken from reports to the National Cancer Institute.

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Li S., 2006	CFOBT (chemical) and IFOBT (immunochemical) were performed simultaneously on all samples, the data for SFOBT was generated hypothetically based on the 2 test results (CFOBT and IFOBT) Colonoscopy was performed on all the participants after the FOBT tests	To perform a direct comparison of the cost-effectiveness of the 3 FOBT protocols (CFOBT, IFOBT and SFOBT) for Chinese patients in an effort to determine the optimal method and number of samples needed for population-based colon cancer screening in China. Diagnostic accuracy study with prospective recruitment (multicenter) and cost analysis	324 patients (186 males; mean age 53.47±15.3) undergoing colonoscopy in 5 major hospitals in Beijing, China from November 2003 to February 2004. For each patient, 3 consecutive stool samples were collected for simultaneous CFOBT and IFOBT tests, followed by colonoscopic examination.	Sensitivity, specificity, Cost per each cancer (in a hypothetical screening population of 100000 subjects with CRc prevalence of 50 per 100000)	**Cost/cancer(Yuan)** Two-sample setting CFOBT=92.0 IFOBT=33.9 SFOBT=19.1 Three-sample setting CFOBT=157.4 IFOBT=80.3 SFOBT=45.5 **Sensitivity** Two-sample setting *Adenoma* +IFOBT (%) vs +CFOBT(%): 28(46.7) vs 25 (41.7) *Cancer* +IFOBT (%) vs +CFOBT(%): 43(87.8) vs 38(77.5) *Adenoma+cancer* +IFOBT (%) vs +CFOBT(%): 71(65.1) vs 63(57.8) Three-sample setting *Adenoma* +IFOBT (%) vs +CFOBT(%): 29(48.3) vs 27 (45.0) p<0.05 *Cancer* +IFOBT (%) vs +CFOBT(%): 47(95.9) vs 47(95.9) *Adenoma+cancer* +IFOBT (%) vs +CFOBT(%): 76(69.7) vs 74(67.9) **Specificity by colonoscopic findings** Two-sample setting *Normal* +IFOBT (%) vs +CFOBT(%): 5(96.4) vs 16 (88.5) *Colitis &haemorrhoid* +IFOBT (%) vs +CFOBT(%): 42(44.0) vs 35(53.3) *Normal/colitis/haemorrhoid* +IFOBT (%) vs +CFOBT(%): 47(78.0) vs 51(76.2) Three-sample setting *Normal*	**III** Overall, IFOBT with two-sample testing showed compatible sensitivity and specificity to the three-sample testing, and had a lower relative cost per cancer detected than the three-sample testing. In conclusion, the new Hemosure IFOBT with two consecutive stool samples appears to be the most cost-effective approach for colon cancer screening.

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
					+IFOBT (%) vs +CFOBT(%): 15(89.2) vs 34 (75.5) p<0.05 *Colitis &haemorrhoid* +IFOBT (%) vs +CFOBT(%): 47(37.4) vs 41(45.3) *Normal/colitis/haemorrhoid* +IFOBT (%) vs +CFOBT(%): 62(71.0) vs 75(64.9)	

Quality assessment: prospective recruitment, spectrum of patients representatives of the patients who will receive the test in practice; patients selection criteria clearly described; same reference standard for all patients; execution of the index test clearly described.

Execution of the reference standard clearly described.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion
Parekh M., 2008	To reappraise stool-based colorectal cancer screening in light of changing test performance characteristics, lower test cost and increasing colorectal cancer care costs. Cost-effectiveness analysis USA	Beginning at age 50 years, average-risk persons progress through the model for 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect US life table data	With Markov model, the study compared Faecal DNA testing every 3 years Annual FOBT or FIT And colonoscopy every 10 years.	Most cost effective strategy	**Cost effectiveness of F-DNA testing (cost/life-year gained), $** Interval: 3 vs 4 years=39200 2 vs 3 years=52600 Compared with no screening, all strategies reduced CRC incidence and mortality **Cost effectiveness** Incremental life-year gained per 100 000 person FIT vs F-DNA version 1 : 2076 FIT vs F-DNA version 1.1: 1219 FIT vs FOBT : 919 FIT vs F-DNA version2: 747 FOBT vs F-DNA version 1 : 1157 FOBT vs F-DNA version 1.1: 300 FOBT vs F-DNA version 2: 172 Incremental cost per life-year gained FIT more effective and less costly over all other strategies Faecal occult blood testing and FIT were preferred over all F-DNA versions. F-DNA version 2 vs FOBT: $ 669 000 **Sensitivity analyses** F-DNA strategies compared more favourably but still cost >$50000 As the sensitivity for large adenoma of the F-DNA version 2 test improved, this strategy became progressively more effective than FOBT. With a sensitivity for large adenoma of 80%, F-DNA version 2 cost $87 500/life-year gained compared with FOBT, but this incremental cost/life-year gained rose sharply as sensitivity for large adenoma decreased. At a test cost of $200, F-DNA version 2 cost <$50 000/life-year gained compared with FOBT when F-DNA test sensitivity for large adenoma was >60%	As novel biological therapies increase colorectal cancer treatment costs, faecal occult blood testing and faecal immunochemical testing could become cost-saving. The cost-effectiveness of faecal DNA testing compared with no screening has improved, but faecal occult blood testing and faecal immunochemical testing are preferred to faecal DNA testing when patient compliance is high. Faecal immunochemical testing may be comparable to colonoscopy every 10 years in persons adhering to yearly testing.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion
					Faecal DNA testing version 2 cost $100 000 . life-year gained vs. faecal immunochemical testing when per-cycle compliance with faecal immunochemical testing was 22%. Faecal immunochemical testing with excellent compliance was superior to colonoscopy every 10 years.	

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Pickhardt 2007	To assess the potential harms, benefits, and cost-effectiveness of Computer Tomography Colonography screening without the reporting of diminutive lesions (≤ 6mm) compared with other screening strategies A mathematical Markov model was constructed and simulation was perfor hypothetical cohort of 100,000 subjects at average risk for CRC cost-effectiveness study	Hypothetical cohort of 100,000 subjects at average risk for CRC. Subjects were evaluated with standard testing every 10 years beginning at age 50 years and covering 3 decades to 80 years of age. CTC screening was modelled for 2 discrete strategies: no polyp size reporting threshold and a 6-mm polyp size reporting threshold. CTC. Source of clinical data and costs not reported	Computed Tomography Colonography without the reporting of diminutive lesions (≤ 6mm) compared with Flexible sigmoidoscopy, colonoscopy	Clinical efficacy of a screening test was defined according to the reduction in CRC incidence vs no screening. Cost-effectiveness of a screening test was assessed based on the additional costs required to gain an additional life year in comparison with either no screening or another screening strategy. One screening strategy was considered dominant over another when it was both less expensive and more clinically effective. Both future costs and future life-years saved were discounted using an annual rate of 3%	**Clinical efficacy** Reduction in CRC incidence predicted by the model. FS: 31.4% Colonoscopy 40.4% CTC without a polyp size threshold: 37.8% CTC with a polyp size threshold: 36.5% **Cost effectiveness**: all screening tests were found to be cost-effective compared with no screening. Primary colonoscopy was the most expensive approach at $9180 per life-year gained compared with $7407 for FS and $7138 for size threshold. CTC with a 6-mm reporting threshold was found to be the most cost-effective approach at $4361 per life-year gained. Compared with primary colonoscopy screening, this approach resulted in a 77.6% reduction in invasive endoscopic procedures and 1112 fewer reported colonoscopy -related complications from perforation or bleeding.	CTC with nonreporting of diminutive lesions was found to be the most cost-effective and safest screening option evaluated, thereby providing further support for this approach. Overall, the removal of diminutive lesions appears to carry an unjustified burden of costs and complications relative to the minimal gain in clinical efficacy

Author, publication year	Study Objective Study Design	Characteristic of participants	Index test Reference standard	Outcome	Results	Conclusion Level of evidence
Sieg 2009	To evaluate the feasibility of CCE for CRC screening in a community practice of gastroenterology. 8 e procedure was aimed at shorter transit times as in most ambulatory practices same day CCE readings and colonoscopies are not practical. Secondary objectives were the eB cacy of colon cleaning and the detection rate of colon neoplasia by CCE compared with colonoscopy. Cross-sectional diagnostic accuracy study	38 patients between 18 and 75years of age scheduled for screeningcolonoscopy or with positive faecal occult blood test (FOBT) without abdominal complaints	Index test: Pill Camm capsule endoscopy Reference standard: colonoscopy	Sensitivity and specificity in detecting significant lesion: polyps larger than 6 mm and carcinomas.	There was only one signi7 cant lesion, a carcinoma in the transverse colon that was identified by CCE and colonoscopy Polyps <6 mm were found in 12 subjects by eitherof the methods, 7 by CCE and 11 by colonoscopy	**III** CCE appears to be a promising new modality for colonic evaluation and may increase compliance with CRC screening. To achieve a short colon transit time, sodium phosphate seems to be a necessary adjunct during preparation. The short transit time is a prerequisite to abandon the delay mode of the capsule. With an undelayed PillCam COLON capsule, a " pan-enteric " examination of the gastrointestinal tract would be possible. Further studies are needed to improve the cleanliness, especially in the rectum and to evaluate the method as a potential screening tool.

Quality assessment: prospective recruitment; spectrum of patients representative of the individuals who will receive the test in practice; patients selection criteria clearly described; verification by reference standard of all subjects; execution of the index and comparator tests adequately described; execution of the reference standard described; independent and blind interpretation of index test and reference standard results: not reported; withdrawal from the study: 2 patients.

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Song 2004	To estimate the clinical and economic consequences of faecal DNA testing vs. conventional CRC screening. Using a Markov model, we estimated CRC incidence, CRC mortality, and discounted cost/life-year gained for screening by faecal DNA testing (F-DNA), faecal occult blood testing (FOBT) and/or sigmoidoscopy, or colonoscopy (COLO) in persons at average CRC risk from age 50 to 80 years cost-effectiveness study	Hypothetical cohort of 100,000 subjects 50-80 years at average risk for CRC. Clinical data on diagnostic accuracy of Faecal DNA drawn from the scientific literature searched on Medline	Faecal DNA testing (F-DNA), compared with: no screening, faecal occult blood testing (FOBT) sigmoidoscopy (FS) every 5 years, FOBT and FS combined colonoscopy every 10 years(COLO)	discounted cost/life-year gained for screening by faecal DNA testing (F-DNA), faecal occult blood testing (FOBT) and/or sigmoidoscopy, or colonoscopy (COLO)	Compared with no screening, F-DNA at a screening interval of 5 years decreased CRC incidence by 35% and CRC mortality by 54% and gained 4560 life-years per 100,000 persons at $47,700/life-year gained in the base case. However, F-DNA gained fewer life-years and was more costly than conventional screening. The average number of colonoscopies per person was 3.8 with COLO and 0.8 with F-DNA. In most 1-way sensitivity analyses and Monte Carlo simulation iterations, F-DNA remained reasonably cost-effective compared with no screening, but COLO and FOBT dominated F-DNA. Assuming faecal DNA testing sensitivities of 65% for CRC and 40% for large polyp, and 95% specificity, a screening interval of 2 years and a test cost of $195 would be required to make F-DNA comparable with COLO reduction in invasive endoscopic procedures and 1112 fewer reported colonoscopy -related complications from perforation or bleeding.	Faecal DNA testing every 5 years appears effective and cost-effective compared with no screening, but inferior to other strategies such as FOBT and COLO. Faecal DNA testing could decrease the national CRC burden if it could improve compliance with screening, particularly where the capacity to perform screening colonoscopy is limited.

Author, publication year	Study Objective Study Design	Characteristic of participants	Index test Reference standard	Outcome	Results	Conclusion Level of evidence
Van Gossum 2009	To assess the diagnostic performance of Pill Camm colon capsule endoscopy for the detection of colorectal polyps and cancers. Cross-sectional diagnostic accuracy study	320 patients (mean age 58.5 years) scheduled to undergo a colonoscopy because they were either known to have colonic disease (patients ≥18 years of age) or suspected of having colonic disease (patients ≥50 years of age). The cohort of patients with known colonic disease included patients with a history of colorectal cancer or adenomatous polyps for whom at least 3 years had passed since their last colonoscopy, patients with any positiv colon on the basis of radiographic examinations, and patients with known ulcerative colitis. In the cohort of patients with suspected colonic symptoms: rectal bleeding, hematochezia, melena, a recent change in bowel habits, or a positive faecal occult-blood test.	Index test: Pill Camm capsule endoscopy Reference standard: colonoscopy	Sensitivity and specificity for colorectal polyps and cancer	**Polyp** Any size Sensitivity 72 (68–75) Specificity78 (71–84) <6 mm Sensitivity 61 (57–64) Specificity 82 (76–87) ≥6 mm Sensitivity 64 (59–72) Specificity 84 (81–87) ≥10 mm Sensitivity 60 (51–66) Specificity 98 (96–99) **Adenoma** ≥6 mm 71 Sensitivity (58–76) Specificity 82 (79–84) ≥10 mm Sensitivity 64 (54–72) Specificity 97 (96–99) **Advanced adenoma** Any size Sensitivity 85 (73–93) Specificity 50 (48–51) ≥6 mm Sensitivity 73 (61–83) Specificity 79 (77–81) ≥10 mm Sensitivity 64 (54–72) Specificity 97 (96–99) **Colorectal cancer** Sensitivity 74 (52–88) Specificity 74 (72–75)	**III** the colon can be visualized with capsule endoscopy, without the need for sedation or air insufflation. However, the sensitivity of capsule endoscopy is lower than the sensitivity of colonoscopy for detecting colonic polyps and adenomas

Quality assessment: prospective recruitment; spectrum of patients representative of the individuals who will receive the test in practice; patients selection criteria clearly described; verification by reference standard of all subjects; execution of the index and comparator tests adequately described; execution of the reference standard described; independent and blind interpretation of index test and reference standard results: yes for index test and reference standard; 8 patients withdrawn from the study, reasons reported.

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Vjian 2007	To estimate the cost-effectiveness of screening with CT colonography The model is a Markov state-transition model based on the natural history of colorectal cancer. cost-effectiveness study	The simulated cohort is distributed in initial states at age 50 based on adenoma and cancer prevalence studies. The cohort moves through the model states based on progression rates derived from studies of the natural history of colorectal cancer: rates of adenoma incidence and prevalence, general mortality rates, and cancer incidence as detailed below. For the purposes of our analyses, we assumed that screening began at age 50 and continued through age 80, though the cohort was modeled to age 100. The main sources of the estimates for natural history were colonoscopic screening studies and autopsy studies for the prevalence of adenomas (15–19) and surveillance, epidemiology and end-results (SEER) registry data for the incidence and mortality rates of colorectal cancer	CT colonography : Compared with : No screening, Colonoscopy We identified 39 studies evaluating the diagnostic accuracy of CT colonography; we used data from a recent meta-analysis of these studies to provide primary estimates of diagnostic accuracy Test compliance was assumed to be 60% The costs of screening tests and interventions were taken from the 2003 Medicare reimbursement schedule	Discounted cost/life-year gained for screening by faecal DNA testing (F-DNA), faecal occult blood testing (FOBT) and/or sigmoidoscopy, or colonoscopy (COLO)	CT colonography every 5 or 10 yr was effective and cost-effective relative to no screening. Optical colonoscopy dominates 2-dimensional CT colonography done every 5 or 10 yr. Optical colonoscopy is weakly dominant over 3-dimensional CT colonography done every 10 yr. 3-D CT colonography done every 5 yr is more effective than optical colonoscopy every 10 yr, but costs an incremental $156,000 per life-year gained. Sensitivity analyses show that test costs, accuracy, and compliance are critical determinants of incremental cost-effectiveness. 3-D CT colonography every 5 yr is a dominant strategy if optical colonoscopy costs 1.6 times more than CT colonography. However, optical colonoscopy is a dominant strategy if the sensitivity of adenomas is 83% or lower.	CT colonography is an effective screening test for colorectal neoplasia. However, it is more expensive and generally less effective than optical colonoscopy. CT colonography can be reasonably cost-effective when the diagnostic accuracy of CT colonography is high, as with primary 3-dimensional technology, and if costs are about 60% of those of optical colonoscopy. Overall, CT colonography technology will need to improve its accuracy and reliability to be a cost-effective screening option
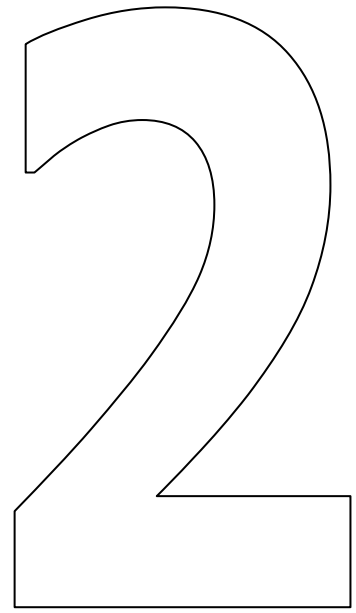
Organisation
EVIDENCE

EU CRC Guidelines Literature Group

2.1 Effectiveness of centrally organised vs. non-organised screening programmes

2.1.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 1

Is organised screening for colorectal cancer offered to the asymptomatic general population age 50 years and older more effective than non organised screening (opportunistic screening or case finding) in reducing colorectal cancer incidence and mortality and in improving coverage and equity? (the first question for chapter one overlaps with this one. Thus the two questions have been combined).

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older (if scientific literature about colorectal cancer screening is not available other condition as breast cancer or cervical cancer can be searched)
I: Organised screening with FOBT or FS: screening where access is not spontaneous but organised or invited in some way.
C Opportunistic screening
O: Colorectal cancer incidence, colorectal cancer mortality**,** Coverage: proportion of eligible population who actually performs the test
Equity: no difference in covered population for social class or socio-economic level
Respect of recommended intervals between tests
S: (Systematic reviews of) RCTs, cohort studies, case-control studies, Controlled clinical trial, Controlled before and after study, time series analysis.

SEARCH METHOD

We weren't able to define a search strategy by key-words or mesh terms specific enough to retrieve an appreciable number of references because of the lack of specific mesh Terms for this topic in the databases. We therefore used the function "related articles" with articles specific on this topic already known by us. So we used the results of studies assessing the impact of organised screening programmes compared with non organised for other pathological condition (colorectal cancer, cervical cancers, breast cancer). Finally we didn't apply a limitation for years of publication because of the paucity of literature available on this topic.

RESULTS

We found 17 articles that seemed relevant from title and abstracts. After reading the full text 13 articles were included in our review. We found one systematic review (6), seven cross-sectional surveys (2, 4, 5, 7, 8, 9, 10), two case control studies (1, 14), two time series analyses (3, 13) and

two prospective cohort studies (11, 12). Only four studies (7, 8, 9, 10) were on colorectal cancer screening. The systematic review aimed at reviewing the existing literature about organised screening. It is of low methodological quality because it doesn't specify how many studies were retrieved and how many included in the review, it doesn't specify the study designs of included studies and does not assess their methodological quality. Finally it doesn't describe accurately the studies and doesn't report their results. In any case the review didn't find or report any studies on organised screening for colorectal cancer.

Only three primary studies were conduced in the USA, the others were conducted in Europe.

Four cross-sectional surveys evaluated physician recommendations on CRC testing and/or the relative compliance.

The probability of not receiving a GP recommendation for CRC screening was highest among Afro-American populations, those with poor access to healthcare and those with a low socioeconomic status (7, 8, 9).

The French study (10) showed that greater compliance with reduced inequalities in the distribution across social groups was achieved in geographical departments where screening was organised by health authorities.

Seven (1-4, 11-13) out of the primary studies retrieved assessed the change in coverage and/or in the incidence of cancer for Pap smear screening. The two cross-sectional surveys (2, 4) assessed the increase in coverage due to the introduction of organised screening versus the pre-existing opportunistic one. Both found an increase of coverage (17% and 23%).

A decrease in the incidence rate of invasive cervical cancer in women who received organised, compared to those having opportunistic screening was also observed in a cohort study (11).

The case control study (1) assessed the difference in invasive cancer incidence among women who had organised (179 women) and spontaneous screening (507 women). The study is of good methodological quality. Results show that invasive cancer incidence rate in lowers in women who received organised screening (0.38 vs 0.82).

A 20% decrease in incidence of fully invasive cervical cancer was observed in an Italian prospective cohort study (12), among women invited to an organized program, compared with those not invited, after introduction of the programme in an area in which intensive opportunistic screening was previously conducted.

The two time series analyses were of good methodological quality.

The first (3) assessed the change in trend of incidence rate of invasive cervical cancer and of coverage 3 years before and 5 years after the organised screening introduction. It found a decrease of incidence rate of invasive cancer of 22% respect to the period before the screening and an increase in coverage of 8.4%. The second (13) assessed the coverage and change in age trend of incidence rate and mortality of invasive cervical cancer before and after introduction of a national call and recall system for cervical cancer screening. Results show an increased coverage from 42% to around 85%; an increase of incidence rate of 35% and a mortality up to one third lower for women aged 25-34 years.

Two studies evaluated the impact of organized breast cancer screening.

The cross-sectional survey (5) assessed the impact of the following variables on type of mammography screening (organised vs opportunistic): stage of adoption: precontemplation, contemplation, action (one mammogram done), maintenance of mammography screening (every two years); knowledge of mammography screening, attitudes towards screening. It is a cross-sectional survey with 932 participants conducted in Switzerland. The study found that women who had an organised screening (vs opportunistic) were more likely to be in precontemplation, to have less favourable attitudes toward mammography, to perceive their financial situation as difficult, were less likely to have visited a gynaecologist or a GP. Moreover women who choose organised screening have less experience with screening, less favourable attitudes towards screening, tended to ignore

screening efficacy. These women were more likely to have never been screened or to be at risk of abandoning screening. Authors concluded that these results support the notion that organised programmes of cancer screening assure a better coverage of hard-to-reach populations.

The case-control study (14) showed that the introduction of breast cancer screening programmes was associated with a reduction in breast cancer mortality attributable to the additional impact of service screening over and above the background spontaneous mammography activity. Compared to not yet invited, women invited in the organised programmes showed a 25% reduction of the risk of breast cancer death.

CONCLUSIONS

The study about CRC screening found that the probability of not receiving a GP recommendation for CRC screening test was highest among those with a low socioeconomic status and that greater compliance with reduced inequalities in the distribution across social groups was achieved in geographical departments where screening was organised by health authorities. (LEVEL OF EVIDENCE V).

All the retrieved studies found that organised screening for pap smears obtained an increase in coverage and a reduction in invasive cancer incidence. (LEVEL OF EVIDENCE III, IV, V)

The studies on mammography found that organised screening assures a better coverage of hard-to-reach populations (LEVEL OF EVIDENCE V) and the service screening is associated with a reduction in the probability of dying for breast cancer (LEVEL OF EVIDENCE IV).

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2.1.2   Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Nieminen 1999	Organised pap smear screening; invitation letter for the screening every 5 years including the place, date and time for taking the smears. Control intervention: spontaneous pap smear screening	Case control	Cases: Incident case of invasive cervical cancer :n.179 Controls: sample from the general population: n:1.507 Information on receiving organised vs spontaneous screening obtained by questionnaire Finland	Incidence of invasive cervical cancer	Adjusted OR for cancer incidence Organised screening: 0.38 (CI95% 0.26-0.56) Spontaneous: 0.82 (CI95%0.53-1.26)	IV pap smears taken in the organised screening have a larger effects on invasive cervical carcinoma compared with spontaneous screening

Quality assessment: definition of the cases by record linkage; consecutive or obviously representative series of cases; Control selected from the general population; adjustment for major potentials confounding (age, socio-economic status, parity, smoking); Exposure ascertained by interview; not specified if the interviewer was blind to case/control condition; Same method of ascertainment for cases and controls; non responders rates described

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Bos 1998	Organised pap smear screening Control intervention: spontaneous pap smear screening	Cross-sectional survey	Random sample of general population over 16 years Information on receiving organised vs spontaneous screening obtained by questionnaire. N:5.773 The Netherlands	Coverage rate	Coverage rate (at least one pap smears in the last five years) for organised screening: 91% opportunistic screening: 68%	V an organised screening programme is required to ensure large coverage

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Nygard 2002	Organised pap smear screening; letter sent to the women inviting to call to her MG or gynaecologist but without an appointment fixed.	Time series analysis	general population over 16 years Information on receiving organised vs spontaneous screening obtained by questionnaire. N:4.744.967 pap smears from over than 1.4 million women Norway	Trends in Incidence rate of invasive cervical cancer 3 years before and 5 years after the screening introduction Change in coverage	Incidence rate of invasive cancer: 22% lower than in the period before the screening Increase in coverage : 8.4%	**IV** the coordinated screening programme provides a low cost way of increasing the coverage and consequently has reduced the rate of invasive cervical cancer

Methodological quality: the intervention occurred at a clearly defined point in time; 3 or more data points before and 3 or more data points recorded after the intervention; Not specified if the intervention was independent from other changes; the intervention itself was unlikely to affect data collection (sources and methods of data collection were the same before and after the intervention); the outcome variables are objective

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Ronco 1997	Organised pap smear screening; letter sent to the women with an appointment fixed. Reminder was sent to non-attenders	Cross-sectional survey	Random sample of attenders and non attenders obtained by computers screening files. Women contacted by telephone interview asking about their previous participation in spontaneous screening N:175 attenders, 347 mom attenders Italy	Increase in coverage	Interviews completed with 83% of the sample Overall coverage (spontaneous + organised). 74% (CI95%71%-78%) Increase in coverage attributable to the organised screening: 17% (CI95% 15%-20%)	**V** an organised screening program is able to increase coverage to a level of 74%. Part of the increase over time is attributable to a spontaneous trend; however, the direct effect of invitation determined an increase of 17%

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Chamot 2007	Organised Mammography screening vs opportunistic screening	Cross-sectional survey	Women aged 40-69 years Information about screening participation, organised vs spontaneous participation, stage of adoption , knowledge and attitude obtained by questionnaire N:932 Switzerland	Screening participation Type of screening: organised vs opportunistic Independent variables: Stage of adoption: precontemplation, contemplation, action (one mammogram done), maintenance on a mammogram screening (every two years) Knowledge of mammography screening, Attitudes towards screening	Women who had an organised screening (vs opportunistic) were more likely to be in precontemplation, to have less favourable attitudes toward mammography, to perceive their financial situation as difficult, were less likely to have visited a gynaecologist or a GP. Women who choose organised screening have less experiences with screening, less favourable attitudes towards screening, tended to ignore screening efficacy. These women were more likely to have never been screened or to be at risk of abandoning screening.	**V** these results support the notion that organised programmes of cancer screening assure a better coverage of hard-to-reach populations.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Madlensky 2003	organised screening programmes	Systematic review	Studies that referred to organised screening programmes and/or compared organised vs non organised screenings	Effectiveness of organised screening programmes	Number of included studies not reported. Very few of the retrieved studies assessed the impact of organised screening; the majority only described the interventions. Most of the studies pertained on cervical cancer screening	Level of evidence not definable because the study design of included studies is not described Conclusions: There is a substantial body of literature on organised cancer screening programmes. However the studies tended to describe programs rather than evaluate their effectiveness. More research is needed that directly compare organised vs opportunistic screening

Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	MEDLINE (1966-6/2002), search of references of retrieved studies
	Date restriction	Up to june 2002
	any restriction	Not specified
Selection	Inclusion and exclusion criteria	Studies that referred to organised screening programmes and/or compared organised vs non organised screenings
Validity assessment	Criteria and process used	Validity assessment of primary studies not perfomed
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Descriptive review. Meta-analysis not performed because of the heterogeneity of included studies
Results Trial flows	Trial flow and reason for exclusion	NO
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies not reported. Only narrative description of some studies
Study results	Descriptive data for each trial	No
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Klabunde C.N., 2006	To design and evaluate interventions that might increase CRC screening use in the Medicare population. Cross-sectional survey North and South Carolina	Random sample of Medicare consumers residing in North and South Carolina with no history of CRC and aged between 50 and 80 years. (N=1901) Telephone interview about CRC status, knowledge, and screening behaviours	CRC screening knowledge and behaviours.	Coverage: proportion of Medicare consumers who performs the test according a physician recommend ation	**Medicare consumers reporting physician recommendation for any colorectal cancer test (%, 95%CI)** Overall = 72.0 (69.8-74.1) By Race White = 77.1 (74.7-79.5) Black = 55.2 (50.9-59.4) By Medicaid eligibility Yes = 66.5 (60.3-72.7) No = 72.7 (70.4-75.0) By Education <High school = 69.2 (64.9-73.5) High school graduate = 71.2 (67.4-74.9) >High school= 85.0 (82.1-88.0) By HealthCare Access: Has usual source of care Yes = 75.2 (73.0-77.3) No = 19.1 (11.1-27.2) Routine/preventive care visit in past 12 months Yes = 7.1 (73.9-78.2) No = 38.9 (31.8-45.9) Logistic regression model: **Predictors of receiving a physician recommendation for any colorectal cancer test (OR, 95%CI)** Race White=1.00 Black = 0.48 (0.37-0.63) p<0.05 Education <High school =1.00 High school graduate = 0.95 (0.70-1.30) >High school= 1.95 (1.40-2.73) p<0.05 Medicaid eligibility No = 1.00 Yes = 1.02 (0.70-1.48)	**V** Individuals with low socioeconomic status and compromised healthcare access were less likely to report a physician recommendation for CRC screening. This study's results showing a lack of knowledge/awareness of CRC screening among Medicare consumers who had never been tested parallel recent findings from the general population, and highlight the need for educational interventions targeting consumers who are not using the benefit.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					HealthCare Access: Has usual source of care No = 1.00 Yes = 3.39 (1.81-6.34) p<0.05 Routine/preventive care visit in past 12 months No = 1.00 Yes = 2.83 (1.84-4.35) **Medicare consumers reporting not having CRC procedures because "Doctor didn't order the test" (%, 95%CI)** FOBT=22.5 (18.8-26.1) Sigmoidoscopy = 22.6 (19.0-26.3) Colonoscopy = 28.1 (24.2-31.9)	

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Brawarsky P., 2004	To explore 1. patient characteristics that are associated with receipt of physician recommendation and subsequent compliance with recommendation 2. the combined effect of recommendation and compliance on CRC testing, defined as an FOBT within the past year, sigmoidoscopy within the past 5 years or colonoscopy within the past 10 years. Cross-sectional survey Massachusetts, USA	Adults aged 50 and older from two surveys (data were linked by a unique code assigned to each record). People was contacted by telephone interview about the effect of physician recommendation and compliance with recommendation on testing. N=779	Physician recommendation on CRC testing (FOBT, sigmoidoscopy, colonoscopy).	Recommendation (proportion of all respondents who received a physician recommendation; compliance (proportion of respondent receiving a physician recommendation who had the recommended test); testing (proportion of all respondents who had the recommended test)	**CRC Recommendation, %** 75.1 95% CI: 72.1-78.1 **CRC Compliance, %** 81.0 95% CI: 78.0-84.4 **CRC Testing, %** 61.0 95% CI: 57.5-64.4 Multiple regression models (OR adjusted for age, education and gender): **Recommendation, % OR** Inadequate health insurance 58.7 % OR=0.45 (95%CI: 0.27-0.78) Household income (US $) 35,000: 70.0 % REF 35,000-74,999: 73.7% OR=1.7 (95%CI: 1.1-2.6) 75,000+: 83.9% OR=3.7 (95%CI: 1.9-6.9) HMO member[1]: 79.5% OR=1.7 (95%CI: 1.1-2.5) Have primary doctor: 77.0% OR=3.1 (95%CI: 1.8-5.4) **Compliance, % (ADJ OR 95% CI)** Inadequate health insurance 83.8% OR=1.4 (95%CI: 0.57-3.6) Household income (US $) 35,000: 84.8% REF 35,000-74,999: 79.4% OR=0.87 (95%CI: 0.47-1.6) 75,000+: 77.9% OR=0.89(95%CI: 0.42-1.9)	**V** Differential rates of CRC testing are related to differences in both physician recommendation of tests and patient compliance with recommendation, and are associated with a variety of patient characteristics. Physicians should be consistent in recommending and encouraging all adults age 50 and older to undergo timely CRC testing. In making these recommendations, physicians should be aware that some groups may be less likely to adhere than others.

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[1] HMO member: commercial, Medicare, Medicaid health insurance.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					HMO member: 80.7 % OR=1.2 (95%CI: 0.74-2.1) Have primary doctor: 81.4% OR=1.7 (95%CI: 0.72-4.0) **Testing (ADJ OR 95% CI)** Inadequate health insurance 49.2% OR=0.64 (95%CI: 0.38-1.1) Household income (US $) 35,000: 59.7% REF 35,000-74,999: 58.5% OR=1.3 (95%CI: 0.86-2.0) 75,000+: 65.3% OR=2.0(95%CI: 1.2-3.5) HMO member: 64.2% OR=1.5 (95%CI: 1.0-2.1) Have primary doctor: 62.8% OR=2.9 (95%CI: 1.6-5.0) Race and education were not associated with recommendation, compliance or testing	

Author, publication year	Intervention	Study design	Study Participants	Outcome	Results	Level of evidence Conclusions
Schenck A.P 2006	Attitude of subjects about CRC test. CRC test use among Whites vs CRC test use among African American	Cross-sectional survey	Random sample of Medicare consumers from urban and rural areas of two states (North and South Carolina), aged 50-80 years, white or African American and with no history of CRC. (N=1901) Telephone interview about knowledge, awareness, and use of CRC tests. North and South Carolina	Compliance (CRC test use)	**Test frequency, weighted % (95%CI)** Never tested Whites 24.2 (21.7- 26.6) vs African Americans 46.8 (42.6- 51.1) Some CRC tests but not current with Medicare covered intervals Whites 19.0(16.7- 21.2) vs African Americans 14.1 (11.1- 17.1) Tested current with Medicare covered intervals Whites 56.8(54.0- 59.7) vs African Americans 39.1 (34.9- 43.3) **Association between African American race (compared to white) and CRC test use, OR (95%CI)** (OR adjusted for sociodemographic characteristics, healthcare access and CRC risk status) Tested according to Medicare covered intervals Not Current : Referent Current: 0.82 (0.63-1.06) Among those not current with tests, no tests compared to any test No test : Referent Any test: 0.48 (0.33-0.70) Among those current with tests, FOBT compared to endoscopy FOBT only : Referent Endoscopy only: 3.06 (1.70-5.51) **Predictor of Medicare Consumers' CRC test use, OR adjusted (95% CI)** Model: current compared to not current Race White: Referent African American: 0.82 (0.63-1.06)	**V** This study found substantial differences in CRC test use rates by race: African American consumers were less likely to have been tested than whites. Removing the racial difference (i.e., equal education, equal access to health services, equal CRC risk status), African Americans and whites have similar test use rates. Until such time, differential use of CRC tests by race will remain an important area for monitoring.

Author, publication year	Intervention	Study design	Study Participants	Outcome	Results	Level of evidence Conclusions
					Education High school or less: Referent Post high school: 1.82 (1.44-2.31) Usual source care No: Referent Yes: 2.27 (1.10-4.69) Checkup last year No: Referent Yes: 2.80 (1.75-4.48) Model: some tests compared to never tested Race White: Referent African American: 0.48 (0.33-0.70) Education High school or less: Referent Post high school: 1.67 (1.15-2.42) Usual source care No: Referent Yes: 6.96 (1.80-26.91) Checkup last year No: Referent Yes: 2.16 (1.27-3.67)	

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Eisinger 2008	To provide a snapshot of cancer screening procedures in France in CRC indications. Cross-sectional survey France	Representative sample of subject living in France department (with o without CRC screening program) and aged 40-74 years (N=970) Representative sample of French GPs (N=178). Telephone interview about attitude and behaviour regarding colorectal cancer screening.	Attitude of subjects and GPs about CRC screening. Department with organised Screening program vs Department without organised screening program	Coverage: % of subjects performing at least 1 screening test for CRC Probability of being screened (%)	**Coverage, N (%)** 240 (25%) **Coverage by presence of screening organisation** with organised screening programs= 34% without organised screening programs= 20% OR=1.99(95% CI:1.47-2.69) (p<0.01) **Coverage by age of organised program** More than 18 months ago=37% About 12 months ago=26% OR=1.76 (95% CI:1.06-2.93) (p<0.03) **Probability of being screened (%)** Univariate analyses Subjects with organised screening Either FOBT or endoscopy: 59% (p<0.01) Not screened: 30% With FOBT + endoscopy: 64% (p<0.01) Not screened: 30% **Probability of being screened (OR 95% CI)** Model 1 (either FOBT or endoscopy) Living in Paris or suburb=0.37 (015-092) Living in the 22 departments with organised screening programs=3.89 (2.52-5.98) Model 2 (FOBT±endoscopy) Living in the 22 departments with organised screening programs=3.91(2.49-6.16) **% GPs who systematically recommended a test** Organised department 29% non organised department 13% (p<0.01)	**V** CRC screening is improved in geographical departments where it is organised by health authorities. In France, an organised screening programs decrease inequalities for CRC screening.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					More than 18 months ago=30% About 12 months ago=26% OR=1.20 (95% CI:0.58-2.51) (pns)	

Author, publication year	Condition	Study objective Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Lynge E., 2006	Screening for cervical cancer. organised screening vs opportunistic screening	To assess the impact on cervical cancer incidence and mortality of opportunistic screening compared with organized screening. Prospective cohort study Copenhagen, Denmark	Women aged 30-64 years and lived in 16 Denmark counties with different screening strategies.	Coverage, Cervical cancer incidence and mortality	30 years (1973-2002)	**Coverage, %** (period 1985-89; organized county: Bornholm, opportunistic county: Vestsjaelland)) <u>Women aged 15-22 years</u> Organized 23% vs opportunistic 53% <u>Women aged 23-30 years</u> Organized 83% vs opportunistic 83% <u>Women aged 30-50 years</u> Organized 88% vs opportunistic 69% <u>Women aged 50-60 years</u> Organized 59% vs opportunistic 38% **Incidence** (counties with organized screening started late vs early) Period 1973-77: 1.87 vs 1.71 Period 1978-82: 1.51 vs 1.26 Period 1983-87: 1.27 vs 0.94 Period 1988-92: 1.15 vs 0.93 Period 1993-97: 0.85 vs 0.74 Period 1998-02: 0.67 vs 0.69 Significant interaction between type of county and calendar period for incidence (p=0.0151) **Mortality** (counties with organized screening started late vs early) Period 1973-77: 0.68 vs 0.66 Period 1978-82: 0.58 vs 0.54 Period 1983-87: 0.45 vs 0.38 Period 1988-92: 0.37 vs 0.31 Period 1993-97: 0.24 vs 0.21 Period 1998-02: 0.24 vs 0.24 No significant interaction between type of county and calendar period for mortality (p=0.9593).	**III** Organisation of cervical cancer screening accelerated the decline in cervical cancer incidence, compared with the trend in areas relying on opportunistic screening. No impact could be measured of the screening organisation on cervical cancer mortality. A decade long stop of an organized screening programme was associated with a temporary increase in cervical cancer incidence and mortality. Coverage remains a key quality indicator in the ongoing modernisation of screening technology.

Author, publication year	Condition	Study objective Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
						No significant interaction when a comparison was made between a single county in which an organized programme was interrupted for an 11-year period and other counties (for incidence p=0.3749 and for mortality p=0.6786). Significant increased incidence and mortality rates at the restart of the organized programme.	

Quality assessment: Exposed cohort truly representative of the women population at average risk of cervical cancer in Denmark; Non exposed cohort drawn from the same community as the exposed cohort; Ascertainment of exposure by clinical records; The outcome was present at the start of the study for some patients; Adjustment for the most important factor (age); Assessment of outcome by record linkage; Complete follow-up

Author, publication year	Condition	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Ronco G, 2005	Screening test for cervical cancer. invited vs not invited	Prospective cohort study	Female Turin inhabitants aged 25-69 years. Invited: for a Pap-test with 3-years intervals for screen-negatives vs not invited Invited attenders: invited with at least one cytology in the organised programme vs invited non attenders Turin, Italy	Cervical cancer incidence	June 1992-December 1998	**Crude incidence (cancer case/10^5 py)** Not invited 118/1265075=9.3 Invited 72/918862=7.8 Invited non attenders 61/570186=10.7 Invited attenders 11/348676=3.2 **Age-standardised incidence** Not invited 8.6 Invited 6.9 Invited non attenders 9.5 Invited attenders 3.0 **IDR (Age-adjusted incidence density ratio incidence)** Not invited 1.0 Invited 0.81 95% IC: 0.59-1.09 Invited non attenders 1.0 Invited attenders 0.25 95% IC: 0.13-0.50	**III** We observed a 20% incidence reduction among invited vs uninvited women. In our population, the largest overall reduction in cervical cancer incidence would be obtained by further increasing attendance in the organised programme and by improving compliance to follow up

Quality assessment: Exposed cohort truly representative of the women population at average risk of cervical cancer in Turin; Non exposed cohort drawn from the same community as the exposed cohort; Ascertainment of exposure by clinical records; The outcome was not present at the star of the study for the non exposed group; Adjustment for the most important factor (age); Assessment of outcome by record linkage; Complete follow-up

Author, publication year	Intervention	Study Objective Study design	Participants	Outcome	Results	Level of evidence Conclusions
Quinn M., 1999	Organised cervical cancer screening; national call and recall system in 1988	To assess the impact of screening on the incidence of and mortality from cervical cancer. Time series analysis England	Women aged over 19 years Age specific incidence and mortality before introduction organised screening vs after introduction organised screening	Age specific trends in Incidence rate of invasive cervical cancer and carcinoma in situ; Age specific trends in mortality. Change in coverage (% of women aged 25-64 who had had a smear test in the previous 5 years)	**Coverage (%)** In 1988: 42% In 1994: 85% Major increasing for older women (55 to 64 years). **Registration rate of carcinoma in situ (case)** In 1971: 10/100000 (2100 cases) In 1995: 80/100000 (20000 cases) Registrations of in situ disease increased broadly in parallel with the numbers of smears taken. Registrations for older groups were consistently low and fell with age. **Incidence rate of invasive cancer (case)** 1971-1985: 14-16/100000 (on average 3900 cases a year) In 1995: 10/100000 35%lower than 1985 The incidence (in 1990 and 1995) in every age group from 30-34 to 70-74 was and significantly lower—by on average 9/100 000 (110 cases). **Mortality (deaths)** In 1950: 11.2/100000 (2500 deaths) In 1987: 6.1/100000 (1800 cases) In 1997: 3.7/100000 (1150 cases) Difference between the projected and actual mortality in women aged 35-54 in 1997. Mortality in 25-34 age group in 1997 was one third lower than in 1985.	**IV** The national call and recall system and incentive payments to general practitioners increased coverage to around 85%. This resulted in falls in incidence of invasive disease in all regions of England and in all age groups from 30 to 74. The falls in mortality in older women were largely unrelated to screening, but without screening there might have been 800 more deaths from cervical cancer in women under 55 in 1997.

Methodological quality: the intervention occurred at a clearly defined point in time; 3 or more data points before and 3 or more data points recorded after the intervention; the intervention was independent from other changes; the intervention itself was likely to affect data collection (changes in death certification: proportion of deaths ascribed to"cancer of the uterus, site unspecified"); the outcome variables are objective; completeness of data set

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Puliti D., 2008	To evaluate the effectiveness of service screening programmes in reducing breast cancer mortality in the Italian areas participating in the IMPACT study. Case control study (multicenter) Italy	Cases: Breast cancer death occurred in the Italian region not later than December 2002 (n=1750) Controls: sample of women (free of breast cancer) from municipality list matched by area of residence and date of birth with 4 controls for each case (n=7000) Women aged 50-74 years resident in the five regions between the year before the start of service screening and 2001 Breast cancer death vs women free of breast cancer	Breast cancer death among screening status of women; screening histories: screening invited or not yet invited, screened or unscreened.	Coverage, risk of breast cancer death, risk of breast cancer	**Invitation status: invited, %** Cases 37.5 Controls 39.6 **Invitation status: not yet invited, %** Cases 62.5 Controls 60.4 **Never screened among invited, %** Cases 54.8 Controls 38.0 **Detection rates** Screen-detected, % Cases 10.3 Not screen-detected with at least 1 screening test,% Cases 6.6 Never respondent detected,% Cases 20.6 Not yet invited detected ,% Cases 62.5 The logistic conditional estimate for **risk of breast cancer** OR (invited vs not yet invited): 0.75 (95%CI:0.62-0.92) OR (screened vs unscreened): 0.50 (95%CI:0.42-0.60) No difference in the risk among age group. OR (screened vs never responded): 0.46 (95%CI:0.38-0.56) OR (screened-self selection corrected vs never responded): 0.55 (95%CI:0.36-0.85) The logistic conditional estimate for **risk of dying for all causes** OR (invited vs not yet invited): 0.83 (95%CI:0.70-0.98) OR (screened vs unscreened): 0.63 (95%CI:0.55-0.73)	**IV** The results of this study show that service screening is associated with a 25% reduction in the probability of dying for breast cancer by allocation to screening invitation and with a 45% reduction when comparing screened with never-respondent women after correction for selection bias.

Quality assessment: definition of the cases by record linkage with the cancer registry; consecutive or obviously representative series of cases; Control selected from local municipality list; adjustment for screening status and age; Exposure ascertained by screening database; Same method of ascertainment for cases and controls; Non respondent described

2.2 Public information campaign

2.2.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 2

Are public information campaigns for organised and non-organised colorectal cancer screening offered to asymptomatic general population aged 50 years and older effective in improving uptake and equity?

CLINICAL QUESTION 3

Which strategy is more effective in improving coverage and equity?

PICOS (FOR BOTH)

P: General population asymptomatic for colorectal cancer aged 50 years and older receiving organised or non organised screening (if scientific literature about colorectal cancer screening is not available other condition as breast cancer or cervical cancer can be searched)
I: Public information campaign on screening (media- TV, cinema, radio, press, internet- meeting places-market, church, different sources of campaign (government, vs. charities vs. commercial etc)
C: **N**o intervention; different campaigns
O: Coverage : proportion of eligible population who actually performs the test
Equity : no difference in covered population for social class or socio-economic level
S: (systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, interrupted time series analysis

SEARCH METHOD

In the first instance systematic reviews have been searched. Because no reviews have been found, we searched primary studies published since 2000.

Search strategy:

Pubmed: ("Health Promotion"[Mesh]) AND ("Mass Screening"[Mesh]) AND ("Colorectal Neoplasms"[Mesh]) AND (("2000/01/01"[PDat] : "3000"[PDat]))

Embase: exp Colon Tumour/ AND exp Cancer Screening/ AND exp Health Promotion/ (Limited to 2000-2008)

Cochrane Library: we searched relevant reviews in the Effective Practice and Organisation of Care (EPOC) Review Group Database

RESULTS

With the bibliographic search we found in MedLine 53 Results. When th systematic review filter was applied there were NO results. We found in Embase 79 Results. After duplicates were removed there were 122 results in total.

After reading title and abstract only one article was considered relevant and included in our review. In the EPOC Cochrane Group database we found one relevant systematic review not specific on to the CRC screening.

The included study (1) is an interrupted time series analysis assessing the impact of a celebrity promotional campaign made by a TV anchor woman on a TV show. She underwent a live, on-air colonoscopy on a TV show. This event was the corner stone of a weeklong series promoting CRC screening. The methodological quality of the study was good: it was specified that the intervention occurred at a clearly defined point in time. There were 3 or more data points before and 3 or more data points recorded after the intervention. The intervention occurred independently of other changes over time. Sources and methods of data collection were the same before and after the intervention. The outcome variables are objective. The study found that the anchor woman TV colon cancer awareness campaign was temporally associated with an increase in colonoscopy rates. Authors concluded that these results suggest that a celebrity spokerperson can have a substantial impact on public participation in screening programmes.

The Cochrane systematic review (2) assessed the effectiveness of intervention based upon the use of mass media, including radio, television, newspapers, magazines, leaflets, posters and pamphlets (alone or in conjunction with other interventions), targeted at the population level and aimed to promote or discourage the use of health care interventions/procedures, or to change public lifestyles. The methodological quality was good. Search strategy was performed on Cochrane EPOC group database, Embase, MedLine , published SR, hand search of relevant journal in the field up to 1996. Included studies were randomised controlled trials (RCTs), controlled before and after studies (CBA) and interrupted time series (ITS) studies. It included 20 time series analyses and one controlled before-and-after study. Only one study was specific to colorectal cancer screening. The review supports the view that mass media campaigns may have a positive influence upon the manner in which health services are utilised while the effect on promoting cancer screening is less clear.

CONCLUSIONS

Only one study and one not up-to-date systematic review have been retrieved. From these studies it seems that promotional campaigns using the media could have a positive impact on health service utilisation but firm conclusions cannot be drawn on CRC screening. (LEVEL OF EVIDENCE IV)

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2.2.2   Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Cram 2003	Celebrity promotional campaign made by an TV anchor woman on a TV show. She underwent a live, on-air colonoscopy on a TV show. This event was the corner stone of a weeklong series promoting CRC screening.	Interrupted time series analysis	General population aged 30-64 years. 95.000 colonoscopies performed during the study period n. 44..269 subjects USA	Colonoscopy rates obtained by the Clinical Outcome Research Initiative (CORI) (voluntary consortium of 400 gastrointestinal endoscopists at 42 site in 22 states) and by the Midwestern managed care organisation databases	Data from 20 months before to 9 months after the celebrity TV show	CORI data. The colonoscopy rates increased immediately after the television campaign; it increased from 14.6 procedures per physician per months to 18.6 P:<0.001. The fitted regression analysis demonstrated an immediate and sustained impact of the celebrity show after adjusting for an underlined trend. The significant increase was sustained for 9 months. However the slope of the fitted line did not change significantly, suggesting that there was a one-time effect of the show but that the general rate of increase remained constant. MCO data These data confirmed the CORI data . To further validate these data, PSA and mammography rates in the MCO were analysed. There was no evidence of concurrent rise in PSA whereas the rates of mammography decreased significantly after the show	IV The anchor woman TV colon cancer awareness campaign was temporally associated with an increase in colonoscopy rates. These results suggest that a celebrity spokerperson can have a substantial impact on public participation in screening programmes .

Quality assessment: The intervention occurred at a clearly defined point in time. There were 3 or more data points before and 3 or more data points recorded after the intervention. The intervention occurred independently of other changes over time. The intervention itself was unlikely to affect data collection : sources and methods of data collection were the same before and after the intervention. The outcome variables are objective. Completeness of data sets: not specified.

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusion
Grilli 2001	Intervention based upon the use of mass media, including radio, television, newspapers, magazines, leaflets, posters and pamphlets (alone or in conjunction with other interventions); were targeted at the population level; and which aimed to promote or discourage the use of health care interventions/procedures, or to change public lifestyles	Cochrane review Meta-analysis of Randomised controlled trials (RCT), controlled before and after studies (CBA) and interrupted time series (ITS) studies.	20 time series analyses and one controlled before-and-after study met the inclusion criteria	changes in health services utilisation	Not specified	All the campaigns relied on the use of a variety of media, including radio, television, newspapers, posters and leaflets. Electronic media, such as the Internet, were not used in any of the studies. All the studies apart from one concluded in their reports that mass media was effective. The effect of mass media campaigns on promoting cancer screening was less clear. While all of the studies reported statistically significant increases in utilisation based on a before-and-after comparison of means , re-analysis using time series regression observed statistically significant changes in level in only four studies and a significant change in slope in only one study	**IV** This review supports the view that mass media campaigns may have a positive influence upon the manner in which health services are utilised while the effect on promoting cancer screening is less clear. Note: studies specific on colorectal cancer: 1

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	COCHRANE EPOC GROUP DATABASE, EMBASE, MEDLINE , PUBLISHED SR, HAND SEARCH OF RELEVANT JOURNAL IN THE FIELD
	Date restriction	Up to 1996
	any restriction	No Language restrictions
Selection	Inclusion and exclusion criteria	Randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before-and-after studies (CBAs) and interrupted time series analyses (ITSs) which were based upon the use of mass media, including radio, television, newspapers, magazines, leaflets, posters and pamphlets (alone or in conjunction with other interventions); were targeted at the population level and which aimed to promote or discourage the use of health care interventions/procedures, or to change public lifestyles but providing information on the subsequent changes in health services utilisation
Validity assessment	Criteria and process used	Validated checklist
Data abstraction	Process used	Two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	regression coefficients corresponding to two standardised effect sizes for each study: a change in level immediately after the introduction of the intervention, and a change in slope
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes (Meta-analysis performed)

2.3   Barriers to participation in screening

2.3.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 4

Which are the barriers which limit the participation to screening programmes?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older
I: Organised Colorectal cancer screening
C: Not applicable
O: Barriers , limitation to participation
S: Cohort studies, cross-sectional studies

SEARCH METHOD

In the first instance systematic reviews have been searched. Because no reviews have been found, we searched primary studies published since 2000.

Search strategy:

Pubmed: ("Health Promotion"[Mesh]) AND ("Mass Screening"[Mesh]) AND ("Colorectal Neoplasms"[Mesh]) AND (("2000/01/01"[PDat] : "3000"[PDat]))

Embase: exp Colon Tumour/ AND exp Cancer Screening/ AND exp Health Promotion/ (Limited to 2000-2008)

RESULTS

With the bibliographic search we found in MedLine 53 Results When Systematic review filter was applied there were NO results. We found in Embase 79 Results. After duplicates were removed there were 122 results in total.

After inspection of titles and abstracts 20 articles were retrieved in full text for further evaluation. 14 fulfilled the inclusion criteria and have been included in the review.

We found eight cross-sectional surveys and one case-control study.
9 studies were conducted in USA, five in Europe.
All studies assessed the percentage of people complying with screening and the factors associated with compliance or non compliance.

Overall, the number of subjects included across all studies were 109.470 (range 111-61.865), all the studies included people aged 50 years or older.

Five studies (1,5,9,11,12) assessed factors associated with compliance with all types of screening (FOBT, FS, colonoscopy), four studies (2,4,6,7)only to FS, three only (3,13,14) to FOBT, one (8)to FOBT and FS and one(10) to FOBT and colonoscopy.

All but three studies(2,7,10) reported the percentage of people adherent to screening. Compliance rates were very heterogeneous across studies: for FOBT it ranged from 16% to 70.8%, for FS it ranged from 10% to 76% (median 30%), for colonoscopy it was around 20%. Two studies reported the compliance rate for all screening modalities and it was 44% and 43% respectively.

Socio-demographic factors associated with compliance:

Age was considered in 10 studies and 5 found an association between older age and participation.

Sex was considered by 6 studies and 3 found higher compliance among men than women.

Level of education was considered by 8 studies and 5 found an association between higher education and compliance.
Marital status was considered in one study; those married had higher attendance rates than single person, divorced or widowed.

Socioeconomic deprivation was considered by 5 studies and 4 founded an association between social deprivation and low compliance.

Care for own health (have a mammogram, cholesterol check, GP visit, go to dentist) was considered by 3 studies and 2 found an association with higher compliance.

Working status was considered by 4 studies and all founded an association between not working and low compliance.

No insurance coverage was considered by 3 studies and 2 found an association with poor compliance.

Smoking, and alcohol consumption were considered by 3 studies and all found an association with lower compliance.

Logistical barriers: 1 study considered the association between lower compliance and the distance from the test provider.

Physician recommendation: 3 studies considered this factor and all found an association between the lack of physician recommendation and poor compliance.

Psychological factors:
Knowledge of screening was considered by 3 studies and all found an association with better compliance.

Perceived risk of CRC cancer was considered by 5 studies and 3 found an association with better compliance.

Perceived benefits of screening was considered by 7 studies and all but one found an association with higher compliance.

Perceived barriers to screening was considered by 4 studies and all but one found association with poorer compliance.

CONCLUSIONS

Overall the compliance rate of the general population to screening for CRC is low with any type of screening. Support from a partner likely explains the positive association of marriage with screening uptake. Men seem to be more adherent to screening than women. Socio-demographic factors more often associated with poorer compliance are socioeconomic deprivation, low education, not working, poor care for own health and rural areas. Lack of physician recommendation was always associated with poor compliance. Among psychological factors perceived benefits was always associated with

higher compliance. Perceived barriers were not described in detail in the studies which assessed this variable but was associated with poorer compliance. (LEVEL OF EVIDENCE: IV,V).

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2.3.2 Evidence tables

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Slattery 2004	Mass screening for colorectal cancer by sigmoidoscopy	Cross-sectional survey among control groups of two case control studies	Control groups of the study randomly selected from general population n: 2.749 USA	Factors affecting participation to screening by colonoscopy: sex, level of education, body mass index, family history of rectal cancer, alcohol consumption	Sex: F vs M OR 0.7 (CI95% 0.5-0.9) Family history of CRC: Y vs No OR:2.5 (CI95%1.8-3.4) Education: <high school OR 0.5 (CI95%0.3-07) Body mass index: >30 vs <25 OR:1.2 (CI95%0.9-1.6) alcohol consumption: high vs none OR 1.6 (CI95% 1.1-2.2)	V having a family history of CRC, being male and having higher education significantly predict screening

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
McCaffery 2002	Mass screening for colorectal cancer by FOBT	Prospective study without control group nested within a multicentre RCT	Subjects 55-64 years old registered with 53 general practice n: 21.219 Scotland	Association between screening interest, screening attendance and sociodemographic variables: age sex, socioeconomic deprivation	Subjects definitely or probably interested in the offer of screening: 47.2% Age: 61-65 vs 55-60: OR 0.92 (CI95% 0.87-0.98) Sex: M vs F: OR 1.08 (CI95% 1.02-1.14) Socioeconomic deprivation: neighbourhood type; less vs high OR 1.97 (CI95% 1.6-2.4) Subjects who attended to screening among those interested: 62.1% Age: 61-65 vs 55-60: OR 0.93 (CI95% 0.80-1.07) Sex: M vs F: OR 1.18 (CI95% 1.06-1.32) Socioeconomic deprivation: neighbourhood type; less vs high OR 2.34 (CI95%1.88-2.92)	V socioeconomic deprivation was a strong predictor of participation to screening

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Sutton 2000	Mass screening for colorectal cancer by sigmoidoscopy	Prospective study without control group nested within a multicentre RCT	Subjects 55-64 years old registered with general practices and who declared interest in screening n: 2.758 UK	Attendance to screening Sociodemographic factors associated with attendance	Attendance rate: 76.1% Age : 61-65 vs 55-60: OR 1.03 (CI95% 0.87-1.23) Sex: M vs F: OR 1.32 (CI95% 1.1-1.57) Ethnicity (white vs other): OR: 1.26 (CI95% 0.74-2.16) Marital status: married vs no OR 1.34 (CI95% 1.07-1.69) Employment: working vs no: OR 1.32 (CI95% 1.1-1.57) Education: qualification vs no: OR 1.36 (CI95% 1.14-1.48) Housing tenure: owner vs no: OR 1.86 (CI95% 1.46-2.36) Car access : car vs no: OR 1.9 (CI95% 1.47-2.47) Had a mammogram in the previous three years (women): yes vs no: OR 2.56 (CI95% 1.71-3.82) Go to the dentins for regular check-up : yes vs no: OR 1.66 (CI95% 1.35-2.04) Bowel symptoms: yes vs no: OR 1.38 (CI95% 1.1-1.72) Smoking: no vs yes: OR 1.75 (CI95% 1.41-2.17)	V men, home owners, car owners, those in employment, those with educational qualifications, women who had mammogram , non smokers, those who go regularly to dentist were significantly more likely to attend for screening

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Weinberg 2004	Mass screening for colorectal cancer by FOBT, sigmoidoscopy, colonoscopy	Cross-sectional survey	Women aged 50 years and older randomly selected from general population. n: 406 USA	Attendance to screening Sociodemographic and psychological factors associated with attendance	Attendance rate: FOBT: 18% Sigmoidoscopy: 20% Colonoscopy: 21% Factors related to compliance: Older age: OR 1.05 (CI95% 1.02-108) Perceived risk of CRC: OR:1.92 (CI95% 1.19-3.16) Perceptions that screening reduces risk: OR 2.49 (CI95% 2.49 (CI95% 1.45-4.27) Importance to follow guidelines: OR 4.95 (CI95% 2.07-11.90) Fear that screening is painful: OR:0.52 (CI95% 0.32-0.84)	V fear about CRC screening related pain is the strong impediment to screening, whereas positive attitudes about the value of screening were strongly related to compliance

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Wardle 2005	Mass screening for colorectal cancer by sigmoidoscopy	Cross-sectional survey	Population sample 55-64 years old taking part in the UK flexible sigmoidoscopy trial N: 5462 UK	Attendance to screening Sociodemographic and psychological factors associated with attendance	Attendance rate: men: 73.2%, women: 67.4% Factors predictors to attendance: <u>whole sample</u> Older age: OR 0.93(CI95% 0.81-1.06) Deprivation: high vs low: OR 0.45 (CI95%0.39-0.52) Working: yes vs no: OR:1.28 (CI95%1.13-1.47) Marital status: no vs yes: OR: 0.68 (CI95%0.58-0.79) GP visits: one or more vs no: OR 0.72 (CI95%0.63-0.83) Bowel symptoms: one or more vs no: OR 1.36 (CI95%1.14-1.63) Family history of CRC: yes vs no: OR 1.83 (CI95%1.48-2.25) Perceived benefits of screening: OR: 1.11 (CI95% 1.08-1.15) Barriers (not described): OR 0.91 (CI95%0.89-0.92) Bowel cancer worry: OR 1.05 (CI95%0.92-1.09) <u>Men</u> Older age: OR 0.92(CI95% 0.75-1.12) Deprivation: high vs low: OR 0.37 (CI95%0.29-0.46) Working: yes vs no: OR:1.43 (CI95%1.16-1.75) Marital status: no vs yes: OR: 0.63 (CI95%0.49-0.82) GP visits: one or more vs no: OR 0.69 (CI95%0.56-0.85) Bowel symptoms: one or more vs no: OR 1.28 (CI95%0.98-1.66) Family history of CRC: yes vs no: OR 1.40 (CI95%1.03-1.90) Perceived benefits of screening: OR: 1.10 (CI95% 1.05-1.15) Barriers (not described): OR 0.92 (CI95%0.90-0.94) Bowel cancer worry: OR 0.99 (CI95%0.87-1.12) <u>Women</u> Older age: OR 0.94(CI95% 0.79-1.12) Deprivation: high vs low: OR 0.54 (CI95%0.45-0.66) Working: yes vs no: OR:1.05 (CI95%0.88-1.25) Marital status: no vs yes: OR: 0.76 (CI95%0.63-0.93) GP visits: one or more vs no: OR 0.79 (CI95%0.66-0.95) Bowel symptoms: one or more vs no: OR 1.56 (CI95%1.22-1.99) Family history of CRC: yes vs no: OR 2.30 (CI95%1.74-3.05) Perceived benefits of screening: OR: 1.13 (CI95% 1.08-1.17) Barriers (not described): OR 0.90 (CI95%0.88-0.92) Bowel cancer worry: OR 1.04 (CI95%0.94-1.16)	**V** more men than women attended screening. Essentially the same factors determine attendance in men and women: socioecomic deprivation, not being married, not working, more GP visits, no bowel symptoms, no family history of CRC are inversely related to attendance for both sex. The only differential effect were for socioeconomic deprivation and unemployment which decerased male more than female attendance and family history which increased attendance more in women than in men . Authors concluded that the reason of difference attendance should be explained by gender differences in the levels of these factors.

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Montaño 2004	Mass screening for colorectal cancer by sigmoidoscopy	Cross-sectional survey	People 50-64 years old randomly selected from general population. n: 2.728 USA	Psychological factors associated with interest in screening: Attitude/belief about the utility of the test Affect: perception of fear, discomfort, embarrassment and violation of privacy Social influence: influence of partner, family, friend, GP or nurse, written material and media Facilitators/barriers: take time off work, difficulty of getting the test Perceived risk: risk of CRC	Attitude: OR: 2.12 (CI95%1.90-2.35) Affect: OR 1.35 (CI95%1.23-1.49) Social influence :OR 1.38 (CI95% 1.25-1.49) Facilitators: OR 1.34 (CI95%1.22-1.47 Perceived risk : OR: 1.28 (CI95%1.17-1.40)	**V** all five component were significantly associated with interest in screening. Attitude had the strongest correlation while perceived risk had the lowest correlation. Interventions designed to change patient attitude would have the greatest likelihood of increasing patients interest

Author, publication	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Lawsin 2006	Mass screening for colorectal cancer by FOBT, sigmoidoscopy	Cross-sectional survey	African Americans living in East Harlem identified from an ambulatory care centre in an urban hospital N:111 USA	Compliance with CRC screening recommendation Psychosocial factors associated with CRC screening compliance: recommendations Sociodempographic factors Knowledge of CRC screening Physician recommendation Perceived risk of CRC Fatalism Attitudes regarding advantages and disadvantages of screening	Compliance with FS screening: 10% Association with compliance: Age: NS Sex: NS Higher education: p<0.01, Married vs no: NS Income: NS History of cancer: NS Knowledge: p<0.01 Physician recommendation: p<0.01 Perceived risk of CRC: NS Fatalism : NS Attitude pros: NS Attitude cons: NS Commitment to regular screening: p<0.05 Information sharing and communication: NS Thinking beyond oneself: p<0.01 Compliance with FOBT screening: 37% Association with compliance: Age: NS Sex: NS Higher education: NS, Married vs no: NS Income: NS History of cancer: NS Knowledge: p<0.01 Physician recommendation: p<0.01 Perceived risk of CRC: NS Fatalism : NS Attitude pros: NS Attitude cons: p<0.01 Commitment to regular screening: p<0.05 Information sharing and communication: p<0.01 Thinking beyond oneself: NS	**V** compliance was low, but higher for FOBT than FS. Knowledge, physician recommendation, higher education were associated with compliance with screening recommendation

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
James 2002	Mass screening for colorectal cancer by FOBT, sigmoidoscopy, colonoscopy	Cross-sectional survey	Low income African Americans chuech members of rural counties N:397 USA	Compliance with CRC screening recommendation Perceived barriers (not described) to screening Perceived benefits (not described)	Had FS screening in the past five years: 30% Had FOBT in the past year: 23% Ever had FOBT: 55% Had colonoscopy screening in the past five years: 20% Factors associated with FOBT compliance Sex: OR 1.18 (CI95% 0.60-2.34) Age: OR 0.95 (CI95% 0.97-1.03) Education. OR 0.60 (CI95%0.30-1.19) Perceived benefits: OR 1.08 (CI95%0.97-1.20) Perceived barriers: OR 0.91 (CI95%0.86-0.97) Factors associated with FS compliance Sex: OR 0.99 (CI95% 0.51-1.92) Age: OR 1.07 (CI95% 1.04-1.11) Education. OR 0.90 (CI95%0.76-1.08) Perceived benefits: OR 1.11 (CI95%1.01-1.23) Perceived barriers: OR 0.92 (CI95%0.87-0.97) Factors associated with colonoscopy compliance Sex: OR 0.69 (CI95% 0.34-1.39) Age: OR 1.06 (CI95% 1.02-1.09) Education. OR 1.09 (CI95%0.90-1.33) Perceived benefits: OR 1.27 (CI95%1.10-1.48) Perceived barriers: OR 0.95 (CI95%0.90-1.01)	V Compliance with screening was low. Age, sex and education were not associated with screening compliance. Perceived barriers were associated with compliance with FOBT and FS screening but not to colonoscopy Perceived benefits were associated with compliance with FS and colonoscopy but not to FOBT

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Menon 2003	Mass screening for colorectal cancer by FOBT, colonoscopy	Cross-sectional survey	random sample of full time employees N:220 USA	Association with screening participation and Sex, ethnicity, marital status, MD recommendation, communication, barriers, benefits, self efficacy, knowledge, education, fear	Only variables significant in bivariate analysis (p≤0.25) included in logistic regression analysis Factor associated with FOBT in the last year Ethnicity (caucasian vs no): OR 0.35 (CI95% 0.12.1.11) Marital status (married vs no) OR: 0.27 (CI95%0.07-0.99) Perceived barriers: OR 1.33 (CI95%0.47-3.79) Perceived benefits: OR 3.01 (1.08-8.40) Fear (yes vs no) : OR 0.62 (CI95% 0.24-1.63) Factor associated with ever had a FOBT Age: OR 1.09 (CI95% 1.10-1.18) Perceived barriers: OR 3.20 (CI95% 1.33-7.72) Communication (high vs low):OR0.67 (CI95% 0.38-1.56) MD recommendation: (yes vs no):OR 17.27 (CI95%6.72-44.22) Education (low vs high):OR 2.53 (CI95%0.59-10.85) Ethnicity (caucasian vs no): OR 0.26 (CI95%0.08-0.73 Sex (F vs M) OR 0.37 (CI95% 0.15-0.92) Knowledge (high vs low) : OR:2.18 (CI95%0.72-6.58) Self efficacy: OR 1.23 (CI95%0.52-2.93) Factor associated with ever had a colonoscopy: Barriers: OR 1.89 (CI95%0.78-4.56) Benefits: OR 2.53 (CI95%1.06-6.03) Communication (high vs low): OR1.25 (CI95%0.56-2.82) MD recommendation: OR 5,26 (CI95%2.23-12.45 Education: (low vs high): OR1.38 (CI95%0.32-5.94) Knowledge :OR 3.56 (CI95%1.2-10-23) Self efficacy: OR3.68 (CI95%1.47-9.20)	**V** FOBT was significantly associated with having low perceived barriers and provider recommendations, colonoscopy was significant associated with higher knowledge, perceived benefits, provider recommendation

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Dassow 2005	Mass screening for colorectal by FOBT, sigmoidoscopy, colonoscopy	Cross-sectional survey	Women ≥52 years old randomly selected from whose visited their provider in the past 24 months n: 128 USA	Compliance with screening recommendation Association with screening compliance and sociodemographic and psychological aspects	Compliance with screening recommendation: 44% Association of compliance with psycho-social factors. Perceived severity of disease: OR 5.05 (CI95%1.85-13.76) Perceived susceptibility of the disease: OR: 3.85 (CI95% 1.58-9.39) Self efficacy to get the test: OR 2.06 (CI95%0.86-4.96) Response of the test efficacy beliefs: OR 1.18 (CI95% 0.48-2.92) Age (>65vs <65): OR1.10 (CI95% 0.45-2.67) Education (high vs low):OR 0.79 (CI95%0.32-1.99) Insurance (yes vs no): OR: 3.01 (CI95%0.72-12.51)	**V** only perceived severity and susceptibility of he disease were associated with compliance with screening recommendation

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Cokkinides 2003	Mass screening for colorectal cancer by FOBT, sigmoidoscopy, colonoscopy	Cross-sectional survey	Random sample of general population aged 50 years and older N: 61.865 USA	Underutilisation of CRC screening Sociodemographic factors associated with underutilisation: Race, marital status, education, employment, income, drinking behaviour, smoking status, general health, health insurance, not afford to see a doctor, frequency of health checkup	Underutilisaion: never had a screening: Female: 50-54 years: 52.4% 55-64: 42.4% 65-79: 31.4% 80+: 35.3% Male : 50-54 years: 58.1% 55-64: 41.3% 65-79: 30.3% 80+: 35.8% Race F: NS; M:NS marital status: single F:P≤0.001; M:NS education: less than high school: F:P≤0.001; M:P≤0.001 employment: out of work : F:P≤0.001; M:P≤0.001 income: unknown, refused: F:P≤0.001: M:P≤0.001 drinking behaviour: +<31 drinks/month: F:P≤0.001; M:P≤0.001 smoking status: smokers: F:P≤0.001; M:P≤0.001 general health: F: NS; M:NS health insurance: none: F:P≤0.001; M:P≤0.001 frequency of health checkup: never had: F:P≤0.001; M:P≤0.001 cholesterol check: never: F:P≤0.001; M:P≤0.001 mammogram: never: F:P≤0.001 Pap test: never: F:P≤0.001	**V** Having less than high school education , no health insurance, being out of work, not utilizing other preventive services, drinking and smoking are associated with underutilisation of CRC screening

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Malila N., 2007	To describe the implementation of the Finnish colorectal cancer screening programme and to present experiences from the first three years based on feasibility and performance indicators. Cross-sectional survey (within an RCT) Finland	Finnish citizen aged 60-69 years randomised in the screening arm of the Public health Programme for CRC screening. N=52994	Colorectal Cancer Screening. Guiac-based faecal occult blood test with three test cards.	Compliance	First screening round **Compliance, complied/invited (%)** Total= 37514/52994 (70.8%) **Compliance by sex** Men= 16625/26247 (63.3%) Women=26747/20889 (78.1%) **Compliance by gender and marital status** Men Single= 1448/3133 (46.2) Married= 12731/18385 (69.2) Divorced=2088/4090 (51.1) Widow=358/639 (56.0) Women Single=1412/2065 (68.4) Married= 13954/17216 (81.1) Divorced =3450/4758 (72.5) Widow=2073/2708 (76.6) **Compliance by gender and birth cohort, %** Men vs Women 1940=72.1 vs 82.0 1941= 67.5 vs 79.2 1942= 65.6 vs 79.3 1943= 65.8 vs 80.2 1944= 60.6 vs 76.3 1945= 63.3 vs 77.8 1946= 59.3 vs 76.5 Second screening round (2006) **Compliance, complied/invited (%)** Total= 3302/4387 (75,3%)	**V** The implementation of colorectal cancer screening in Finland, measured with attendance and performance of the guaiac-based faecal occult blood test has been successful. The programme also meets the criteria for a randomised trial and for a public health programme allowing unbiased data to be collected during the implementation period.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Giorgi Rossi P., 2005	To analyse self-reported reasons for non compliance, individual and environmental determinants of screening compliance, and the interaction between them. Case control study (nested in a randomised trial) Lazio, Italy	<u>Cases</u>: sample of non compliant trial patients (n=600) <u>Controls</u>: sample of compliant patients (n=600) Half patients were invited for FOBT screening at the hospital and the other half directly at their general practitioner's office.	Faecal occult blood test screening at the hospital or GPs's office. Telephone questionnaires about the reason for compliance or non compliance, logistical ,cultural, psychological and emotional barriers.	Determinants of non compliance	**Determinants of non compliace: Distance from provider (N)** <u>1-15 min</u> Cases: 122 Controls: 301 <u>15-30 min</u> Cases: 44 Controls: 75 <u>>30 min</u> Cases. 21 Controls: 15 <u>m.i.</u> Cases: 40 Controls: 19 OR (95% CI) adjusted by age, gender and provider) 15-30 min vs 1-15 min: 0.8 (0.5-1.3) >30 min vs 1-15 min: 0.3 (0.2-0.7) **Lack of time (N), OR (95%CI)** Cases: 69 Controls: 25 OR adj: 0.2 (0.1-0.3) **Employement status (N), OR (95%CI)** <u>Currently employed</u> Cases: 69 Controls: 91 OR: ref <u>Homemarker</u> Cases: 76 Controls: 223 OR adj: 2.2 (1.3-3.7) <u>Retired</u> Cases: 53 Controls: 81 OR adj: 1.1 (0.6-1.9)	**IV** To increase compliance, screening programmes must make all efforts possible to involve test providers who are geographically close to the target population. Our population suggested one way to overcome logistical and psychological barriers may be to invite all target individuals from a single household or block for testing on the same day.

					Unemployed Cases: 2 Controls: 5 OR adj: 1.8 (0.3-9.6) m.i. Cases: 27 Controls: 10 **Education level (N), OR (95%CI)** 0-4 years of study Cases: 18 Controls: 17 OR: ref 5-7 years of study Cases: 53 Controls: 119 OR adj: 2.5 (1.2-5.2) 8-12 years of study Cases: 35 Controls: 83 OR adj: 2.5 (1.1-5.6) High school graduate Cases: 49 Controls: 117 OR adj: 2.7 (1.3-6.0) university Cases: 27 Controls: 10 OR adj: 2.1 (0.9-5.1) m.i Cases: 48 Controls: 28	

Quality assessment: definition of the cases by compliant patients of RCT; consecutive or obviously representative series of cases; Control selected from non compliant patients of RCT; adjustment for age, gender and provider; Exposure ascertained by GP and arm randomisation of RCT; Same method of ascertainment for cases and controls; Different response rate: cases=356, controls 404; real case and comparable questionnaires=227, real controls and comparable questionnaires=410

2.4 Intervention to reduce barriers

2.4.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 5

Are there effective interventions to reduce barriers to participation?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older (if scientific literature about colorectal cancer screening is not available other condition as breast cancer or cervical cancer can be searched)
I: Any intervention aimed at reducing limitation in participation to screening
C: No intervention
O: Increase in participation
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, interrupted time series analysis

SEARCH METHOD

In the first instance systematic reviews have been searched. Because no reviews have been found, we searched primary studies published since 2000.

Search strategy:

Pubmed: ("Health Promotion"[Mesh]) AND ("Mass Screening"[Mesh]) AND ("Colorectal Neoplasms"[Mesh]) AND (("2000/01/01"[PDat] : "3000"[PDat]))

Embase: exp Colon Tumour/ AND exp Cancer Screening/ AND exp Health Promotion/ (Limited to 2000-2008)

RESULTS

With the bibliographic search we found in MedLine 53 Results We found in Embase 79 Results. After duplicates were removed there were 122 results in total.

After inspection of titles and abstracts 9 articles were retrieved in full text for further evaluation. 6 fulfilled the inclusion criteria and have been included in the review. We found one systematic review and 5 RCTs

Two RCTs were conducted in the UK and two in USA.

Methodological quality: two study (1, 6) had an adequate allocation concealment; in the other studies the method used to conceal allocation was not described. The outcome assessor was blinded in only

two studies (3,6); in the other studies it was unclear. In two studies (1,6) there was an adequate method described to protect against contamination. In the other studies it was unclear.

Three studies (2,3,4), number of participants 3613 (range 119-3185) assessed the effectiveness of different kind of mailed written information materials, one (49 subjects) assessed the effectiveness of an interactive multimedia programme seen at the physician practice while the last (210 Chinese living in US) assessed the effectiveness of a cultural intervention through a health educator. The outcomes were: knowledge, perceived barriers and benefits of screening, perceived risk, interest in screening. Overall, all the studies were efficacious in increasing knowledge about CRC and screening method, but did not have an effect on perceived barriers or benefits and on the intention to be screened but one study (6) underlined that a culturally appropriate intervention significantly increased FOBT screening in a group of low-income and less-acculturated minority patients.

One study (3) found that adding illustrations about polyp-cancer process and the removal of the polyps during FS to written material significantly increased knowledge and understanding.

The fourth study (1) compared an individually tailored interactive multimedia program seen at the physician practice versus the same intervention not individual tailored. The individual tailored intervention seemed more efficacious in increasing readiness to undergo screening.

The systematic review (5) was of good methodological quality. Search strategy was performed on Cochrane EPOC group database (which contains all articles retrieved in Medline), Embase, Healthstar, Cochrane Controlled trial register, previous SR, HCQIP database up to February 1999. Included studies were RCTs and CCTs assessing the effectiveness of reminders for providers and patients, provider feedback, education, financial incentives for providers or patients (reduction in payment or direct compensation), regulatory and legislative actions (legislative actions outside the medical care organisation), organisational change (changes in clinical procedures or facilities and infrastructures), visual materials on screening compliance. It included 19 studies. Results show that the more effective intervention is implementation of specific organisational change that makes identification and delivery of these services a routine part of patient care. Patient reminders can be used in addition to organisational change. Patient financial incentives should also be considered. Education is less effective and should not be the first choice for intervention but interventions that use visual instruments to enhance appeal and clarity are more effective.

CONCLUSIONS

Overall the interventions based on education are not efficacious in improving screening compliance; intervention realised by sending information materials about CRC and screening seem efficacious in increasing knowledge but do not have an effect on other factors (perceived barriers or benefits, intention to be screened). Interventions which use illustration or any visual instrument seem to be more efficacious (LEVEL OF EVIDENCE: I).
Culturally and linguistically appropriate approaches promoting FOBT can enhance screening practice in groups of low-income and less acculturated minority patients (LEVEL OF EVIDENCE: II).

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2.4.2 Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Jerant 2007	1. Interactive multimedia computer programs with personally tailored feedback messages based on patient demographic characteristics, preferences for CRC screening, knowledge, self efficacy, perceived barriers and benefits, stage of readiness for screening. Intervention received at the practitioner study before the visit. Duration 1hour 2. non tailored intervention to encourage CRC screening. Intervention received at the practitioner study before the visit. Duration 1hour	RCT	Random sample of patients aged 50 years and older, able to use a multimedia software and not up-to date for CRC screening n. 49 USA	self report data Knowledge Readiness to undergo screening Perceived barriers Perceives benefits Self efficacy	No follow up: assessment immediately after the intervention	Change of the scores from per to post intervention. Adjusted outcomes of the experimental condition versus control Parameter estimate from linear regression. Self efficacy: 0.23 (CI95% 0.00-0.26) Barriers :-0.22 (CI95%-0.51-0.08 Benefits: 0.08 (CI95%-0.12-0.27) Knowledge: 0.02 (CI95%-1.82-1.87) Readiness (adjusted OR for moving from pre-contemplation to contemplation or planning) OR 5.01 (CI1.13-22.23)	**II** Tailored intervention is more efficacious than non tailored intervention in increasing self-efficacy and readiness to undergo screening

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: unlikely that the control received the intervention; attrition bias: percentage of participants completing the study: 80-100% in each group; detection bias: blinding of outcome assessor: unclear; intention to treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Robb 2006	1. mailed information on risk factors for CRC plus 2. nformation on screening mailed 3. information on risk factors for CRC 4. no intervention Every group received also a questionnaire and a free post replay envelop	RCT	Random sample of general population aged 45-66 years n. 3185 UK	Self report data: Knowledge Emotional impact of the intervention Interest in screening	No follow up: assessment of letter replay	Questionnaire returned by 1945 subjects(61%) Total knowledge score: 1.information on risk factors plus screening:8.15 2.information on risk factors alone: 8.41 3. no leaflet: 4.95 P:0.01 Emotional impact: STAI anxiety mean 1. 10.78(SD3.83) 2. 10.58(SD3.66) 3. 10.66(SD3.79) P: NS Bowel cancer worry: no significant difference across groups Interest in screening: Yes (definitely or probably) 1.92.6% 2. 92% 3. 93.5% No (definitely or probably) 1.7.4% 2. 8% 3. 6.6% P: NS	**II** Knowledge about CRC risk factor increase significantly in the two experimental groups compared with controls. There was no significant difference in anxiety, bowel cancer worry and interest in screening among groups.

Quality assessment: allocation by household; avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: unclear; attrition bias: percentage of participants completing the study: 60-79% in each group; detection bias: blinding of outcome assessor: unclear; intention to treat analysis performed (included subjects who declared tot having read the leaflet).

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Brotherstone 2006	mailed a written leaflet containing information on risk factors for CRC and on FS screening leaflet plus illustration about polyp-cancer process and the removal of the polyps during FS mailed the same written leaflet alone	RCT	Random sample of general population aged 60-64 years n. 318 UK	Telephone Interview planned for a random sample of 123 subjects Good understanding of the preventive aim of FS	follow up: four weeks	Telephone interview performed only with 65 subjects Good understanding: 1. text and pictures: 84% 2. text only:57% 3. adjusted OR: 10.5 (CI95%1.72-68.43)	**II** Simple visual information is effective in increasing understanding of the preventive aims of FS compared to written information alone

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: unclear; attrition bias: percentage of participants completing the study: <59% in each group; detection bias: blinding of outcome assessor: blind to treatment allocation at outcome assessment; intention to treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Lipkus 2003	All received booklet with basic information about CRC, early detection, different screening methods 1. additional information on incidence and risk factors plus additional information on severity of CRC 2. additional information on risk factors only 3. additional information on severity only 4. no additional information	RCT	Subjects recruited by local newspaper advertisement aged 50 years and older and who had not a FOBT in the past two years n. 119 USA	Self report data assessed by telephone interview Perceived risk Perceived severity Intention to be screened	follow up: six months	93 subjects reached at follow up Perceived risk: overall participants increased their perception of risk; there were no difference between groups.: data not shown Perceived severity: perceived severity did not change from pre to post intervention for any groups: data not shown. Screening intentions: participants who received information on risk tended to show greater intention to be screened than patients who did not receive this information: data not shown; other results not reported.	II The study did not show significant differences among groups

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: unclear; attrition bias: percentage of participants completing the study: 60-79% in each group; detection bias: blinding of outcome assessor: unclear; intention to treat analysis not performed.

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusion
Stone 2002	Reminders for providers and patients, Provider feedback, Education, financial incentives for providers or patients (reduction in payment or direct compensation), regulatory and legislative actions (legislative actions outside the medical care organisation), organisational change (changes in clinical procedures or facilities and infrastructures), visual materials	Meta-analysis of RCTs and CCTs.	19 studies,	Compliance with screening (FOBT)	Not specified	Organisational change: OR 17.6 (CI95%12.3-25.2) Provider education: OR 3.01 (CI95%1.98-4.56) Patients reminder: OR 2.75-(1.90-3.97) Patient financial incentives: OR 1.82 (CI95%1.35-2.46) Provider reminder: OR 1.46 (CI95%1.15-1.85) Patient education: OR 1.38 (CI95%0.84-2.25) Feedback for provider :OR 1.18 (CI95%0.98-1.43) High visual appeal and clarity of educational materials: OR 1.95 (CI95%1.24-3.05)	I: systematic review of RCTs the more effective intervention is implementation of specific organisational change that makes identification and delivery of these services a routine part of patient care. Patient reminders can be used in addition to organisational change. Patients financial incentives should also be considered. Education is less effective and should not be the first choice for intervention.

SR Stone 2002
Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	Cochrane EPOC group database(which contains all articles retrieved in Medline), Embase, Healthstar, Cochrane Controlled trial register, previous SR, HCQIP database
	Date restriction	Up to February 1999
	any restriction	Language restrictions not mentioned
Selection	Inclusion and exclusion criteria	RCTs and CCTs assessing the effectiveness of the described intervention on screening compliance
Validity assessment	Criteria and process used	Validated checklist
Data abstraction	Process used	Two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Meta-regression models to calculate adjusted OR
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes (Meta-analysis performed)

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Tu S., 2006	To evaluate a clinic-based, culturally appropriate program that promoted FOBT screening through a health educator among lower-income and less-acculturated Chinese Americans RCT Seattle, Washington	210 Chinese patients from ICHS[2] database (aged 50-78 years) speaking Cantonese, Mandarin and/or English were randomised to receive cultural intervention (intervention: 63.8% female; 59.1% aged between 50 and 64 years) or usual care (control: 61.9% female; 49.5% aged between 50 and 64 years) No difference between groups age, language, insurance, gender and prior screening.	Cultural intervention promoting FOBT screening through: Intervention group: Trilingual and bicultural health educator, bilingual materials(motivational video, CRC motivational pamphlet, informational pamphlet, and an FOBT instructions) and three FOBT cards (n=105). Control group: usual care. (n=105).	Compliance	**Compliance (FOBT screening)** Intervention 69.5% Control 27.6% **FOBT screening participation within 6 months of randomisation** OR adjusted for sociodemografic and prior screening participation Intervention vs ctrl: OR: 6.38 (95%CI=3.44-11.85) Insurance Private vs Public : OR :0.36 (95%CI=0.13-1.00) None vs Public: OR:0.30 (95%CI=0.07-1.31) Age group 50-64 vs 65+:OR. 1.53 (95%CI=0.79-2.95) Gender Female vs Male: OR: 1.08 (95%CI=0.57-2.04)	**II** Culturally appropriate intervention significantly increased FOBT screening in a group of low-income and less-acculturated minority patients. Given the large effect size, future research should determine the effective core component(s) that can increase CRC screening in both the general and minority populations.

Quality assessment: allocation concealment: adequate; performance bias: not applicable; protection against contamination: not clear; attrition bias: lost to follow up not reported; detection bias: blinding of outcome assessor: yes; intention to treat analysis not performed.

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[2] ICHS: International Community Health Services

2.5   Active invitation of target population

2.5.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 6

Which active invitation strategy is more effective in improving participation in colorectal cancer screening among the general asymptomatic population age 50 years and older ?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older
I: Active invitation to screening (letters, appointment, telephone call etc - GP's involvement)
C: Different strategies
O: Coverage : proportion of eligible population who actually performs the test
Equity : no difference in covered population for social class or socio-economic level
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, feasibility studies

SEARCH METHOD

In the first instance systematic reviews have been searched. Because no up to date reviews have been found, we searched primary studies published since 2000.

Search strategy:

Pubmed: ("Health Promotion"[Mesh]) AND ("Mass Screening"[Mesh]) AND ("Colorectal Neoplasms"[Mesh]) AND (("2000/01/01"[PDat] : "3000"[PDat]))

Embase: exp Colon Tumour/ AND exp Cancer Screening/ AND exp Health Promotion/ (Limited to 2000-2008)

Cochrane library: we searched relevant reviews in the Effective Practice and Organisation of Care (EPOC) Review Group Database

RESULTS

With the bibliographic search we found in MedLine 53 Results. We found in Embase 79 Results. After duplicates were removed there were 122 results in total.

After inspection of titles and abstracts 25 articles were retrieved in full text for further evaluation. 19 fulfilled the inclusion criteria and have been included in the review. We also found one systematic review in the Cochrane Library on the effectiveness of any type of reminder to increase the compliance with immunisation programmes.

We found one systematic review (6), 10 RCTs (1-5, 8, 9, 11-13), one CCT (10) and 6 cross-sectional surveys (14-19) and one time series analysis (20). The primary studies were conducted: 7 in USA, 3 in Australia, 8 in Europe and one in China.

Only one primary study wasn't on colorectal cancer screening but on bowel cancer screening (19).

Six RCTs used an adequate allocation concealment method (3,8,9,11-13), for the others it is unclear; blinding of outcome assessor was not a source of bias in five RCTs because the outcome was objective; in the other two (1,4) where outcome was self reported the blindness was unclear. In one RCT (2) there was contamination between two groups which prevent the validity of this comparison. Loss to follow up were not evaluable for the design of the study in one study and less than 10% in the others studies. In the RCTs the number of subjects included across all studies were 61835 (range 313-26682), all but one of the studies included people age 50 years or older at average risk of colorectal cancer. One (4) included first degree relatives of patients with CRC.

Three studies (2, 4, 9) assessed the effectiveness of mailing a written information brochure about CRC and screening modalities on the rate of screening performed or requested versus no intervention. One study (2), in which the GPs were not involved in the intervention did not find an increase in colorectal screening of any type compared to controls. Authors concluded that possible reasons of absence of effect could be the focus of the intervention on education rather than motivation and the requirement that patients interested in screening seek further information and a referral on their own from their providers. The other study (4) where the information brochures were sent by the GPs found a statistically significant increase in the number of screening requests. The third RCT (9) indicates that an advance notification letter increases participation in CRC screening; this effect was explained by a population shift in readiness to undertake screening.

Six studies assessed the effectiveness of mailing FOBT kit and brochure with information, on the rate of screening performed. One study (1) assessed the effectiveness of mailing FOBT kit and brochure with information with or without 3 reminders for non responders versus no intervention. The study found that a direct mail intervention with FOBT kit plus instruction significantly increases the use of FOBT test and of any test. The role of reminders was not statistically significant but there was contamination between groups which biased the results.

Another study (3) assessed the effectiveness of mailing FOBT kit with an invitation letter from a central screening centre versus the same letter with impersonal specification that the practice supported the offer versus an invitation letter sent and signed by the practitioner. The study found that a personalised letter of invitation to screening signed by the practitioner achieves better participation than the same letter sent by a centralised screening centre.

The third study (5) assessed the effectiveness of educational seminars for the physicians, followed by the mailing by the practitioners of a personalized letter, an educational brochure, an FOBT kit with instructions and a stamped returned envelop to their patients versus no intervention. The study didn't find an effect on rates of CRC screening with the exception of an increase in the FS rates over 5 years. An Italian study (11) evaluated the participation in CRC screening through different screening strategies: mailing FOBT kit, FOBT delivered by GP, patient's choice of FOBT or "once-only" sigmoidoscopy, "once-only" sigmoidoscopy or sigmoidoscopy followed by biennial FOBT. Mailing of FOBT kit with instructions, together with the invitation letter and the information leaflet, is effective in increasing the proportion of people completing the FOBT test. Another study (13) evaluated compliance with FOBT screening between mailing FOBT kit versus a direct contact of a trained non health-professional; the results show that the participation can be increased by means of an invitation made through direct contact by a suitably trained non-health professional. The last trial (12) compared mailing an FOBT kit to all non-responders to the initial invitation, with mailing a recall letter with a test order coupon resulted in a substantial decrease in the programme costs, but also in significant decrease in participation.

The Italian randomised trial (8) assessed the role of the general practitioner with an invitation letter sent by GP and with an invitation to be screened at the GP's office versus the same letter but with an

invitation to be screened at the hospital. The authors found that the involvement of GPs in CRC screening can be very effective to enhance the compliance.

Also other types of studies involving GPs assessed the participation rate in CRC screening. A non randomised study (10) compared the compliance after an invitation FOBT letter signed by the Mayor or the GP. Results show that the direct distribution of FOBT kit by general practitioners to their outpatients was associated with the best compliance.

The time series analysis (20) assessed the trend of number of eligible subjects performing FOBT screening in Czech Republic. It found GPs should play a substantial role in CRC screening either by assessing the risk of their patients, explaining the screening options, or by deciding on the most individually-appropriate strategy within their local health care system.

The cross-sectional survey (14) of the Asian population confirmed the significant role of a physician's recommendation in increasing uptake of the screening test: 20% of those undertaking CRC screening had a recommendation by the family physician.

The other three cross-section surveys found that the probability of not receiving a GP recommendation for CRC screening and so the uptake for CRC testing was highest among Afro-American populations (16), those with poor access to healthcare and those with a low socioeconomic status (17,18).

Coverage by a screening programme is also influenced by the GPs attitudes and preferences.

In the French survey (15), factors significantly influencing practitioners' reasons for promoting CRC screening are, by order of importance: the effectiveness of the screening programme, the proportion of false negatives, the proportion of false positives and, to a lesser extent, the annual remuneration for conducting screening. A qualitative survey (19) indicated that GPs needed adequate information prior to recommending a screening programme.

The systematic review specific to CRC screening (6) was of good methodological quality. The search strategy was performed on Cochrane EPOC group database (which contains all articles retrieved in MedLine), Embase, Healthstar, Cochrane Controlled trial register, previous SR, HCQIP database up to February 1999. Included studies were RCTs and CCTs assessing the effectiveness of reminders for providers and patients, provider feedback, education, financial incentives for providers or patients (reduction in payment or direct compensation), regulatory and legislative actions (legislative actions outside the medical care organisation), organisational change (changes in clinical procedures or facilities and infrastructures), visual materials on screening compliance. 19 studies were included. Results show that the more effective intervention is implementation of specific organisational change that makes identification and delivery of these services a routine part of patient care. Patient reminders can be used in addition to organisational change. Patients financial incentives should also be considered. Education is less effective and should not be the first choice for intervention.

The Cochrane review (7) assessed the effectiveness of different kind of reminders (reminder and recall systems delivered by letter, postcard, telephone, autodialer or in person, e.g. provider gives face-to-face reminder). Generic reminders or personal reminders that address issues specific to the patient, one-time or multiple reminders on compliance with immunisation program. The methodological quality was good. Search strategy was performed on MEDLINE (1966-1998), EMBASE, PsychINFO, Sociological Abstracts and CAB Abstract, Cochrane EPOC group database up to December 2004. Included studies were randomised controlled trials (RCT), controlled before and after studies (CBA) and interrupted time series (ITS) studies. It included 43 studies. Results show that all types of reminders were effective (postcards, letters, telephone or autodialer calls), with telephone being the most effective but most costly.

CONCLUSIONS

Any kind of reminder is effective in increasing compliance. Invitation scheme with a personalised letter directly sent and signed by the general practitioner seems to be more effective than impersonal letter

sent by a central screening centre; reminders made by phone call are more effective (LEVEL OF EVIDENCE I). Two studies found that invitation schemes which send the FOBT kit together with the invitation letter are more effective than letter alone. A third study didn't find significant results (LEVEL OF EVIDENCE II). The involvement of GPs or direct contact of a trained non-health professional in screening can be very effective in improving compliance (LEVEL OF EVIDENCE II) but the screening uptake is also influenced by the GPs attitudes and preferences (LEVEL OF EVIDENCE V).

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2.5.2 Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Church 2004	1. mailing of FOBT kits with pamphlet with instruction and information and postage paid return envelop with laboratory address 2. same intervention plus 3 reminders for non responders 3. no intervention	RCT	Random sample of general population aged 50 years and older n= 1,398 USA	Change in self reported overall compliance with screening guidelines (FOBT or FS or BE or Colonoscopy) after the intervention Change in self reported compliance with FOBT	1 year	Self reported compliance change from baseline to year follow up; both mail group vs control: increase of any test use 5.9% (CI95% 0.5%-11.5%) Increase of FOBT use: 18.4% (CI95%12.5%-24.3%) Mail FOBT plus reminder vs Mail FOBT without reminder : increase of any test use: NS Increase of FOBT use: NS	**II** A direct mail intervention with FOBT kit plus instruction significantly increases the use of FOBT test and of any test. The role of reminders are not statistically significant but there was contamination between groups which biased the results

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: contamination happened between mail group with reminder and mail group without reminder: part of the group without reminder did receive it; attrition bias: percentage of participants completing the study: 80-100% in each group; detection bias: blinding of outcome assessor unclear; intention t treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Costanza 2007	1. mailing of brochure with information on CRC and recommendation of annually FOBT and sigmoidoscopy every 5 years or colonoscopy every 10 years. Three months later telephone counselling call (TCC). The GPs were not involved 2. usual care	RCT	Random sample of patients from 37 study practice n. 2806 USA	Completion of FOBT, sigmoidoscopy or colonoscopy for CRC screening by chart audit: % of patients who did the Test in the post TCC period % of patients who did the Test after brochure and before the TCC % of patients who did not the test	22 months	Records audit completed for 2448 patients (87% of the sample) FOBT No test : exp: 88%, ctrl: 90% Test done after brochure and before the TCC: exp:3% ctrl:2% Test done in the post TCC period:exp:9% ctrl:8% SIGMOIDOSCOPY No test : exp: 99%, ctrl: 99% Test done after brochure and before the TCC: exp:4% ctrl:<1% Test done in the post TCC period: exp: 5% ctrl:<2% COLONOSCOPY No test : exp: 86%, ctrl: 85% Test done after brochure and before the TCC: exp:3% ctrl:3% Test done in the post TCC period:exp:12% ctrl:12% ANY TEST No test : exp: 75%, ctrl: 76% Test done after brochure and before the TCC: exp:5% ctrl:5% Test done in the post TCC period:exp:20% ctrl:19%	II The intervention did not increase colorectal screening compared to control. Possible reason of absence of effect could be the focus of the intervention on education rather than motivation and the requirement tha patients interested in screening seek further information and a referral to their own from their providers.

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention; attrition bias: percentage of participants completing the study: 80-100% in each group; detection bias: blinding of outcome assessor: not relevant because objective outcome has been used; intention t treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Cole 2002	1. Invitation to screen from a central screening service without any indication that a GP was involved. 2. invitation to screen from a central screening service and endorsed impersonally by the patient' medical practice by stating that the practice supported this offer 3. invitation to screen sent on medical practice letterhead indicating that the screening was endorsed by the practice and signed by the GP. Letters sent with CRC information sheet and FOBT kit in all groups	RCT	Random sample of patients from 2 primary care practice and the Australian electoral roll n. 2400 Australia	Return rate of completed stool collection devices	12 weeks	Completed stool returned Exp1(invitation form central screening service): 32% (± 3.7%) Exp 2 (invitation impersonally endorsed by practice):38% (±3.9%) Exp 3 (invitation sent and signed by practitioner): 40.1%(±3.9%) Exp1 vs exp3: OR 0.69 (CI95%0.54-0.87) Exp 1 vs Exp2: OR: 0.77 (CI95%0.60-0.98) Exp2 vs Exp 3:NS	**II** Personalised letter of invitation to screening signed by practitioner achieves better participation than the same letter sent by a centralised screening centre.

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention; attrition bias: loss to follow up not reported; detection bias: blinding of outcome assessor: not relevant because objective outcome has been used; intention to treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Harris 2000	1. pamphlet with information about CRC risk , screening test and action for screening and request form for FOBT screening given to the patients by their GP 2. no intervention	Cross over RCT	First degree relatives of patients with colorectal cancer aged 50 years and older n. 303 Australia	Screening request	Six weeks	Screening request: Intervention group: 18% Control group: 4% OR: 4.7 (CI95%1.4-16.7)	**II** The recruitment strategy was effective in increasing first relative of patients with CRC n requesting screening by FOBT. The results could be generalized to general population

Quality assessment: randomisation of GP and then of their patients; avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: unclear; attrition bias: percentage of participants completing the study: 80-100% in each group; detection bias: blinding of outcome assessor unclear; intention to treat analysis not performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Walsh 2005	1. educational seminars for physicians . Then physician sent a personalized letter, an educational brochure, a FOBT kit with instructions and a stamped returned envelop to their patients 2. no intervention	RCT	Patients of randomised GPs aged 50-79 years. n. 94 GPs, n. 9.652 patients USA	Patient colorectal screening rates	5 year	7993 patients followed for 2 years %change in screening rates FOBT: intervention: +11.4% control. +13.1% P:NS ANY TEST Intervention: +12.7% Control: +12.5% P:NS 2665 patients followed for 5 years: FS Intervention: +7.4% Control: +4.4% P:<0.01 COLON: Intervention: +9.5% Control: +9.5%% P:NS ANY TEST Intervention: +9.7% Control: +8.6% P:NS Mean change in screening rates form pre to post intervention (GPs as unit of analysis) FOBT: Intervention : +12.7 (SE 1.9) Control: +15.9 (SE .02) P: NS ANY TEST: Intervention: +12.6 (SE 1.0) Control: +13.7 (SE 1.0)	II the intervention had no effect on rates of CRC screening with the exception of an increase in the FS rates over 5 years .

Quality assessment: block randomisation of GPs; unit of analysis: GPs; avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention; attrition bias: percentage of participants completing the study: 80-100% in each group; detection bias: blinding of outcome assessor: not relevant because objective outcome has been used; intention to treat analysis not performed.

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusion
Stone 2002	Reminders for providers and patients, Provider feedback, Education, financial incentives for providers or patients (reduction in payment or direct compensation), regulatory and legislative actions (legislative actions outside the medical care organisation), organisational change (changes in clinical procedures or facilities and infrastructures), visual materials	Meta-analysis of RCTs and CCTs.	19 studies,	Compliance with screening (FOBT)	Not specified	Organisational change: OR 17.6 (CI95%12.3-25.2) Provider education: OR 3.01 (CI95%1.98-4.56) Patients reminder: OR 2.75-(1.90-3.97) Patient financial incentives: OR 1.82 (CI95%1.35-2.46) Provider reminder: OR 1.46 (CI95%1.15-1.85) Patient education: OR 1.38 (CI95%0.84-2.25) Feedback for provider :OR 1.18 (CI95%0.98-1.43) High visual appeal and clarity of educational materials: OR 1.95 (CI95%1.24-3.05)	I the more effective intervention is implementation of specific organisational change that makes identification and delivery of these services a routine part of patient care. Patient reminders can be used in addition to organisational change. Patients financial incentives should also be considered. Education is less effective and should not be the first choice for intervention.

SR Stone 2002

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	COCHRANE EPOC GROUP DATABASE(WHICH CONTAINS ALL ARTICLES RETRIEVED IN MEDLINE), EMBASE, HEALTHSTAR, COCHRANE CONTROLLED TRIAL REGISTER, PREVIOUS SR, HCQIP DATABASE
	Date restriction	Up to February 1999
	any restriction	Language restrictions not mentioned
Selection	Inclusion and exclusion criteria	RCTs and CCTs assessing the effectiveness of the described intervention on screening compliance
Validity assessment	Criteria and process used	Validated checklist
Data abstraction	Process used	Two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Meta-regression models to calculate adjusted OR
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes (Meta-analysis performed)

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusion
Jacobson 2005	Reminder and recall systems delivered by letter, postcard, telephone, autodialer or in person (provider gives face-to-face reminder). Generic reminders or personal reminders that address issues specific to the patient, one-time or multiple reminders . For immunisation	Cochrane review Meta-analysis of Randomised controlled trials (RCT), controlled before and after studies (CBA) and interrupted time series (ITS) studies.	43 studies,	Immunisation rate	Not specified	Any type of reminder for any type of immunisation: OR 1.66 (CI95%1.46-1.89) Person-to-person telephone reminders OR : 1.92 (CI 95% 1.20, 3.07) Letter reminders :OR 1.89 (95% CI: 1.53, 2.34). Autodialer computerized telephone reminders (OR = 1.43, 95% CI: 1.30, 1.57).	**I** In all settings that were evaluated, patient reminder and recall systems appear to be effective for improving immunisation rates. All types of reminders were effective (postcards, letters, telephone or autodialer calls), with telephone being the most effective but most costly.

SR Jacobson 2005 (Cochrane review)

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE (1966-1998), EMBASE, PSYCHINFO, SOCIOLOGICAL ABSTRACTS AND CAB ABSTRACT, COCHRANE EPOC GROUP DATABASE
	Date restriction	Up to December 2004
	any restriction	English language restriction
Selection	Inclusion and exclusion criteria	Randomised controlled trials (RCT), controlled before-and-after studies (CBA) and interrupted time series studies (ITS) assessing the effectiveness of reminder for immunisation
Validity assessment	Criteria and process used	Validated checklist
Data abstraction	Process used	Two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	OR computed by random effect model
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes (Meta-analysis performed)

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Federici A., 2006	To assess the effect of the provider on the compliance of the 50–74 year-old population in returning the FOBT and to analyse the characteristics of the GP that are associated with high compliance among his beneficiaries. RCT Lazio, Italy	7332 patients (age 50-74) from 13 Lazio districts were randomised to pick up and return FOBT (Guaiac or immunochemical test) at the GP' office (GP group) or at the gastroenterology centre of the hospital (Hospital group). 130 GPs sampled from 13 districts of the Lazio region completing a questionnaire about screening attitudes. No difference between GP group and hospital group for gender, age classes and residence.	Invitation letter for FOBT screening : Signed by GP and with an invitation for patients to pick up and return the FOBT at the GP's office (GP group=3657) or Signed by GP but with an invitation for patients to pick up and return the FOBT at the gastroenterology centre of the hospital (Hospital group=3675) Patients were also randomised to receive two types of screening test: Guaiac (n=3611) or immunochemical (n=3721)	Compliance	**Compliance, % (N)** GP group: 50.3% Hospital group: 16.2 % RR 3.40 (95% CI:3.13-3.70) **Compliance to colonoscopy with positive FOBT** GP group: 69.0% Hospital group: 72.3 % $X^2 = 0.19$; p = 0.66 Statistical association between compliance obtained by a GP in GP arm and compliance in hospital arm ($r^2 = 0.195$; f(1;127) = 30.8; p = $2 \cdot 10^{-7}$) Variability in the compliance among district rho=0.41 95%CI: 0.34–0.49 **Compliance (GP's characteristics influencing compliance), OR (95%CI)** <u>Gender</u> Male 1.00 Female :1.26 (0.94-1.67) <u>Patients visited per day</u> ≤25 : 1.00 >25 : 0.74 (0.58-0.95) <u>Residence</u> Other :1.00 Rome : 0.77 (0.62-0.95) <u>Recommendation of FOBT for CRCS</u> Correct :1.00 Incorrect : 0.76 (0.59-0.97) Not recommending : 0.94 (0.69-1.28)	**II** The compliance to the FOBT with GPs was 3.4 times higher than compliance with the hospital, independent from type of test and geographical area. There was high variability among GPs: GPs with heavy workloads and those who incorrectly recommended FOBT for CRCS obtained lower compliance. The involvement of GPs in the FOBT for screening can be very effective in improving compliance, but the effectiveness is dependent on the willingness of the GP to be involved.

Quality assessment: allocation concealment: adequate; performance bias: not applicable; protection against contamination: it is likely that the control received the intervention; attrition bias: 12 lost because impossibility to contact 1 ill GP; detection bias: blinding of outcome assessor: no

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Cole 2007	To determine the impact of three novel letter-based invitation-to-screen strategies on participation in FIT (faecal immunochemical test) based CRC screening. RCT Adelaide, South Australia	2400 people aged 50-74 years from Australian electoral roll were randomised to one of four CRC screening strategies.	CRC screening invitation strategies with: Control= standard invitation-to-screen letter explaining risk of CRC and the concept, value and method of screening Risk = invitation with additional messages related to CRC risk. Advocacy= invitation with additional messages related to advocacy for screening from previous screening programme participants Advance Notification= first, a letter introducing Control letter messages followed by the standard invitation-to-screen. Invitation included a FIT kit in all groups	Participation rate	**Participation rate** At 12 weeks after invitation Control = 39.5% Advance = 48.3% Risk =40.3% Advocacy =40.3% Advance vs Control= RR 1.23 (95% CI: 1.06-1.43) At 2 weeks after invitation (early participation) Advance = 25.2% Control = 18.2% Advance vs Control= RR 1.38 (95% CI: 1.11-1.73) At 14 weeks after invitation Advance = 48.3% Control = 39.7% Advance vs Control= RR 1.22 (95% CI: 1.05-1.42) Statistical association between age (60–64 years: RR 1.32, CI 1.12–1.56; 65–69 years: RR 1.47, CI 1.23–1.77) and participation and female (RR 1.13, CI 1.03–1.26) participation at week 12.	**II** These results demonstrate that a simple advance notification letter had a significant and positive effect on participation in FIT-based CRC screening. The effect was large and immediate. In contrast, two other interventions were ineffective in promoting participation levels above that of a standard invitation letter. Organized screening programmes should consider using advance notification letters to improve programme participation.

Quality assessment: allocation concealment: adequate; performance bias: not applicable; protection against contamination: it is likely that the control received the intervention; attrition bias: lost to follow up not reported; detection bias: blinding of outcome assessor not relevant because objective outcome has been used; intention to treat analysis not performed.

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Grazzini G., 2000	To evaluate the results of an experimental screening protocol for colorectal cancer by faecal occult blood testing in a municipality of the Province of Florence. CCT Florence, Italy	15235 eligible subjects (7383 males and 7852 females) aged 50-70 years and living in a municipality without a screening program.	Invitation letter for 1 day immunochemical FOBT screening without any dietary restriction: Signed by GP and with the the instruction to pick up the FOBT kit from volunteer centers (group A=4784); Signed by GP but with the instruction to obtain the kit directly from their outpatient clinic (group B=7248) or Signed by the program coordinator and by the Mayor (GPs not recruited or not agree to be involved in the program)and with the instruction to get test kits from volunteer centres (group C=3203)	compliance	**Compliance, %** Overall: 42.1 Group A: 41.5 Group B: 45.5 Group C: 35.4 Group A vs Group B: p<0.001 Group A vs Group C: p<0.001 Group B vs Group C: p<0.001	**II** The study provides useful information about the efficiency and feasibility of a screening program for colorectal cancer using faecal occult blood testing. The study showed that involvement of GPs in colorectal cancer screening effectively improves compliance rates.

Quality assessment: unit of allocation: patient; unit of analysis: patient; allocation concealment: inadequate (according to the choices of GPs; performance bias: no blinding; protection against contamination: it is likely that the control received the intervention; attrition bias: loss to follow up not reported; detection bias: blinding of outcome assessor: no.

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Segnan N, 2005	To assess the participation rate achievable through different strategies using an FOBT and sigmoidoscopy, to evaluate the acceptability and the safety of the proposed tests to the target population, to compare the detection rates of different strategies and to estimate their costs. Multicenter RCT Italy	26682 individuals (aged 55-64 years) from general practitioners' rosters or population registers were randomised to one of five different screening strategies for CRC: FOBT by mail group (46,2% of males; 49,5% aged<60 years), FOBT by GP or screening facility group (48,2% of males; 50,9% aged<60 years), patient's choice group (47,2% of males; 50,6% aged<60 years), once-only sigmoidoscopy group (47,1% of males; 50,9% aged<60 years), sigmoidoscopy +biennial FOBT group (46,1% of males; 49,8% aged<60 years).	Different CRC screening strategies : Biennial FOBT sent by mail (n=2326); biennial FOBT delivered by general practitioner or screening facility (primary care or outpatient clinics) (n=5985); patient's choice of FOBT or " once-only" sigmoidoscopy (n=3631); " once-only " sigmoidoscopy (n=3695); sigmoidoscopy followed by biennial FOBT beginning 2 years after a sigmoidoscopy with negative findings (n=11045). Reminder letter for all non responders. Two additional invitations (at 12 and 24 months) for non responders and allocated to the sigmoidoscopy arms.	Participation rates	**Participation rate, (%)** FOBT by mail: 30.1 FOBT by GP or screening facility: 28.1 Patient's choice: FOBT 14.6 Sigmoidoscopy 12.5 Total 27.1 Once-only sigmoidoscopy: 28.1 sigmoidoscopy +biennial FOBT: 28.1 Total: 28.1 **Increase in participation rate by mailed reminders (%)** FOBT by mail: 9.2% FOBT by GP or screening facility: 11.1% Once-only sigmoidoscopy: 3.3% sigmoidoscopy +biennial FOBT: 3.2% Mail delivery of the FOBT kit:2% **Increase in participation rate by additional invitations at 12 and 24 months (%)** Once-only sigmoidoscopy: 5.9% sigmoidoscopy +biennial FOBT: 5.6% **Participation rate, OR (95%CI)** (OR adjusted by age, sex, center and screening arm) FOBT arm FOBT by GP or screening facility: 1.00 (referent) FOBT by mail: 1.11 (0.99-1.23) 55-59 ys: 1.00 (referent) 60-64 ys: 1.01 (0.92-1.11) Women: 1.00 (referent) Men: 0.82 (0.74-0.90)	**II** Our results also suggest that, during the 2-year period of our study, the proportion of people screened with sigmoidoscopy or with FOBT was similar. The evaluation of the impact of these strategies should therefore take into account their costs and the number of tests required to achieve the same yield of advanced neoplasia. Other crucial aspects to be considered in the implementation and assessment of CRC screening interventions are information about patients' preferences and effective communication between patients and their health care providers about the risks and benefits of CRC screening.

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					<u>Whole study population</u> sigmoidoscopy +FOBT: 1.00(referent) Once-only sigmoidoscopy: 1.00 (0.92-1.09) Patient's choice: 0.95 (0.88-1.04) FOBT by GP or screening facility: 1.00 (0.93-1.07) FOBT by mail: 1.11 (1.00-1.22) 55-59 ys: 1.00 (referent) 60-64 ys: 0.94 (0.89-0.99) Women: 1.00 (referent) Men: 1.05 (0.99-1.10)	

Quality assessment: allocation concealment: adequate; performance bias: no blinding; protection against contamination: it is likely that the control received the intervention; attrition bias: 427 patients lost because undelivered invitations; detection bias: blinding of outcome assessor not relevant because objective outcome has been used

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Tifratene K., 2007	To determine the cost effectiveness of two recall strategies for non-responders to delivery of a faecal occult blood test kit. Randomised controlled trial. Marseille, France	7016 inhabitants of Bouches-du-Rhône aged 50-74 not participating in the medical phase of screening campaign (invitation to consult the general practitioner to delivering the FOBT kit). The non-responders were randomised to conventional group (54.5% of females; mean age 61.3 years) and experimental group (54.6% of females; mean age 61.2 years) No difference between the groups for gender and age.	Recall invitation to screening FOBT for non responders to medical phase using: Conventional group: systematic recall where the test kit was mailed to all non-responders to the first phase (n=3058) Experimental group: a recall letter with an order coupon to request a free test kit. Test kit mailed only to persons who explicitly requested one (n=3058).	Compliance, cost/ effectiveness, incremental cost effectiveness ratio	Actually received the invitation (N) Conventional =3450 Experimental=3457 Test mailed (N) Conventional =3508 Experimental=389 (11.1%) Not performed the test (about response coupon) Conventional =6.4% Experimental=8% p<0.01 Test performed Conventional =14.2% Experimental=7.8% $p<10^{-5}$ No difference in test performing between the groups for gender and age. Test performed (among population eligible), % Conventional = 14.7% Experimental= 8.3% $p<10^{-5}$ Total cost (euros) Conventional= 16424 Experimental= 5013 Cost/effectiveness per 1000 (euros) Conventional= 4681.7/139.4 (33.59) Experimental= 1429.0/77.2 (18.50) Incremental cost effectiveness ratio (euros) Conventional vs Experimental = 3257.8/62.1 (52.34) (=51.24 considering only eligible population)	II Mailing a recall letter with a test order coupon can lead to substantial economy with a lost of participation of 6.4% at the test mailing phase. Our study raises the question of the use of the resources saved by the selective mailing strategy, and of the impact of such use on screening performance. If these resources were invested in improving the population's awareness of the problem and in health education, there might be a significant increase in the participation rate after application of a selective mailing strategy.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					<u>Incremental cost effectiveness ratio (euros)</u> <u>if kit price=2 euros</u> Conventional vs Experimental =40.47 <u>if kit price=1 euro</u> Conventional vs Experimental =26.16	

Quality assessment: allocation concealment: adequate; blindness of patients: no, blindness of staff: no; blindness of outcome assessor: no; lost at follow up: 58 (4 because death and 54 because wrong address) from conventional group and 51 (8 because death and 43 because wrong address) from experimental group

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Courtier R., 2002	To determine the participation rate in a general population sample in Barcelona city, and the degree of correctness of specimen collection, using the standard method of invitation (letter from a health professional), as well as to investigate whether it is possible to increase participation by using the strategy of invitation by means of direct contact through a trained non-health professional. RCT Barcelona, Spain	2026 individuals (aged 50-74 years) enlisted in one primary health care centre with no history of CRC were randomised to: standard group (621 men and 439 women; 598 aged 50-64 years and 462 aged 65-74 years) or study group (568 men and 398 women; 515 aged 50-64 years and 451 aged 65-74 years). No difference between standard group and study group regard to age and sex.	CRC screening invitation strategies by: Standard group=post and subjects were required to return the specimens and questionnaire themselves to a pre-determinate primary health care centre (n=1060); Study group= direct contact of a trained non health-professional who, during a visit, supplied subjects with two containers for collection of specimens on two consecutive days (n=966) Both groups received the same informative materials and self administered questionnaire on medical history.	Participation rate, proportion of inadequate samples	**Participation rate, %** Standard= 36.5 vs Study= 57.7 p<0.001 OR adjusted for age, sex and homes with more than one partecipants=2.40 (95%CI:2.10-2.88) No significant differences in the participation rate according to sex or age group. **Specimen collection correctness, %** Standard= 67.5 vs Study= 75.1 p<0.014 No significant differences in the degree of correctness of specimen collection according to sex or age group.	**II** participation and specimen collection in colorectal cancer screening programmes can be increased by means of an invitation made through direct contact by a suitably trained non-health professional.

Quality assessment: allocation concealment: adequate; performance bias: not applicable; protection against contamination: it is likely that the control received the intervention; attrition bias: none lost at follow up; detection bias: blinding of outcome assessor not relevant because objective outcome has been used

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Sung JJ.Y, 2008	To understand obstacles to the uptake of colorectal tests among Chinese and discuss the possible intervention efforts needed. Cross-sectional survey Hong Kong	Random sample of Chinese residents of Hong Kong aged between 30 and 65 years. (N=1004) Telephone interview about CRC testing according to the Heath belief model (analysing perceived susceptibility, perceived severity, perceived benefit, perceived barriers, and cues to actions.	Knowledge of CRC testing	Compliance	20% of those undertaking CRC screening test had a recommendation by family physician. **Compliance: (%), crude OR (95% CI)** Physician's recommendation No : (5.8) 1.00 Yes : (57.3) 21.82 (12.98-36.69) p<0.001 **Compliance: adjusted OR (95% CI)** Physician's recommendation No : 1.00 Yes : 23.50 (10.66-51.80) p<0.001	**V** Education on CRC symptoms, risk factors, and usefulness of screening tests is crucial. The engagement of lay health advisors and a family physician's recommendation is worthwhile. Strong support from the government and local health authorities holds the key to success in the combat of the rising incidence and mortality by CRC.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Berchi C., 2006	To identify empirically GPs' preferences for different characteristics of a mass CRC screening program using the faecal occult blood (FOB) test with a view to developing incentives for promoting CRC screening. Cross-sectional survey France	Random sample of GPs from 2 types of French department (with organized CRC screening or without organized CRC screening programme). N:294 (700 GPs selected but 294 usable and returned questionnaires) Postal questionnaires about GPs' preference for different alternatives of CRC screening.	GPs' reason for promoting CRC screening. GP randomised to receive one of two version of questionnaire differing in order of presentation of attributes (specific CRC screening organisation).	Factors influencing GPs' reason for promoting CRC screening	**GPs' reasons for promoting CRC screening** (coefficients of regression model with main effect) CRC screening effectiveness 11.4995±0.6524 (p<0.0001) Proportion of false-negative -1.1696±0.3524 (p=0.0009) Proportion of false-positive -1.7025±0.4200 (p=0.0001) Annual remuneration for screening practice 0.000385±0.00012 (p=0.0013) Public information by media 0.1109±0.0976 (p=0.2560) Ordering effect in model -0.0176±0.0521 (p=0.7352)	V factors significantly influencing GPs' resons for promoting screening were: CRC mortality reduction, i.e., the effectiveness of the screening program; the proportion of false-positive results conditioned by the positive predictive value of the screening test; the proportion of false-negative results conditioned by the sensitivity of the screening test; and the amount of annual remuneration for screening practice. Personal and professional characteristics had little influence on GPs' preference.

Author, publication year	Intervention	Study design	Study Participants	Outcome	Results	Level of evidence Conclusions
Schenck A.P 2006	Attitude of subjects about CRC test. CRC test use among Whites vs CRC test use among African American	Cross-sectional survey	Random sample of Medicare consumers from urban and rural areas of two states (North and South Carolina), aged 50-80 years, white or African American and with no history of CRC. (N=1901) Telephone interview about knowledge, awareness, and use of CRC tests. North and South Carolina	Compliance (CRC test use)	**Test frequency, weighted % (95%CI)** Never tested Whites 24.2 (21.7- 26.6) vs African Americans 46.8 (42.6- 51.1) Some CRC tests but not current with Medicare covered intervals Whites 19.0(16.7- 21.2) vs African Americans 14.1 (11.1- 17.1) Tested current with Medicare covered intervals Whites 56.8(54.0- 59.7) vs African Americans 39.1 (34.9- 43.3) **Association between African American race (compared to white) and CRC test use, OR (95%CI)** (OR adjusted for sociodemographic characteristics, healthcare access and CRC risk status) Tested according to Medicare covered intervals Not Current : Referent Current: 0.82 (0.63-1.06) Among those not current with tests, no tests compared to any test No test : Referent Any test: 0.48 (0.33-0.70) Among those current with tests, FOBT compared to endoscopy FOBT only : Referent Endoscopy only: 3.06 (1.70-5.51) **Predictor of Medicare Consumers' CRC test use, OR adjusted (95% CI)** Model: current compared to not current Race White: Referent African American: 0.82 (0.63-1.06)	**V** This study found substantial differences in CRC test use rates by race: African American consumers were less likely to have been tested than whites. Removing the racial difference (i.e., equal education, equal access to health services, equal CRC risk status), African Americans and whites have similar test use rates. Until such time, differential use of CRC tests by race will remain an important area for monitoring.

					Education High school or less: Referent Post high school: 1.82 (1.44-2.31) Usual source care No: Referent Yes: 2.27 (1.10-4.69) Checkup last year No: Referent Yes: 2.80 (1.75-4.48) Model: some tests compared to never tested Race White: Referent African American: 0.48 (0.33-0.70) Education High school or less: Referent Post high school: 1.67 (1.15-2.42) Usual source care No: Referent Yes: 6.96 (1.80-26.91) Checkup last year No: Referent Yes: 2.16 (1.27-3.67)	

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Klabunde C.N., 2006	To design and evaluate interventions that might increase CRC screening use in the Medicare population. Cross-sectional survey North and South Carolina	Random sample of Medicare consumers residing in North and South Carolina with no history of CRC and aged between 50 and 80 years. (N=1901) Telephone interview about CRC status, knowledge, and screening behaviours	CRC screening knowledge and behaviours.	Coverage: proportion of Medicare consumers who performs the test according a physician recommendation	**Medicare consumers reporting physician recommendation for any colorectal cancer test (%, 95%CI)** Overall= 72.0 (69.8-74.1) By Race White = 77.1 (74.7-79.5) Black = 55.2 (50.9-59.4) By Medicaid eligibility Yes = 66.5 (60.3-72.7) No = 72.7 (70.4-75.0) By Education <High school = 69.2 (64.9-73.5) High school graduate = 71.2 (67.4-74.9) >High school= 85.0 (82.1-88.0) By HealthCare Access: Has usual source of care Yes = 75.2 (73.0-77.3) No = 19.1 (11.1-27.2) Routine/preventive care visit in past 12 months Yes = 7.1 (73.9-78.2) No = 38.9 (31.8-45.9) Logistic regression model: **Predictors of receiving a physician recommendation for any colorectal cancer test (OR, 95%CI)** Race White=1.00 Black = 0.48 (0.37-0.63) p<0.05 Education <High school =1.00 High school graduate = 0.95 (0.70-1.30) >High school= 1.95 (1.40-2.73) p<0.05 Medicaid eligibility No = 1.00 Yes = 1.02 (0.70-1.48)	**V** Individuals with low socioeconomic status and compromised healthcare access were less likely to report a physician recommendation for CRC screening. This study's results showing a lack of knowledge/awareness of CRC screening among Medicare consumers who had never been tested parallel recent findings from the general population, and highlight the need for educational interventions targeting consumers who are not using the benefit.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					HealthCare Access: Has usual source of care No = 1.00 Yes = 3.39 (1.81-6.34) p<0.05 Routine/preventive care visit in past 12 months No = 1.00 Yes = 2.83 (1.84-4.35) **Medicare consumers reporting not having CRC procedures because "Doctor didn't order the test" (%, 95%CI)** FOBT=22.5 (18.8-26.1) Sigmoidoscopy = 22.6 (19.0-26.3) Colonoscopy = 28.1 (24.2-31.9)	

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Brawarsky P., 2004	To explore 1. patient characteristics that are associated with receipt of physician recommendation and subsequent compliance with recommendation 2. the combined effect of recommendation and compliance with CRC testing, defined as an FOBT within the past year, sigmoidoscopy within the past 5 years or colonoscopy within the past 10 years. Cross-sectional survey Massachusetts, USA	Adults aged 50 and older from two surveys (data were linked by a unique code assigned to each record). People was contacted by telephone interview about the effect of physician recommendation and compliance with recommendation on testing. N=779	Physician recommendation on CRC testing (FOBT, sigmoidoscopy, colonoscopy).	Recommendation (proportion of all respondents who received a physician recommendation); compliance (proportion of respondent receiving a physician recommendation who had the recommended test); testing (proportion of all respondents who had the recommended test)	**CRC Recommendation, %** 75.1 95% CI: 72.1-78.1 **CRC Compliance, %** 81.0 95% CI: 78.0-84.4 **CRC Testing, %** 61.0 95% CI: 57.5-64.4 Multiple regression models (OR adjusted for age, education and gender): **Recommendation, % OR** Inadequate health insurance: 58.7% OR=0.45 (95%CI: 0.27-0.78) Household income (US $) 35,000: 70.0 REF 35,000-74,999: 73.7 OR=1.7 (95%CI: 1.1-2.6) 75,000+: 83.9 OR=3.7 (95%CI: 1.9-6.9) HMO member[3]: 79.5 % OR=1.7 (95%CI: 1.1-2.5) Have primary doctor: 77.0 % OR=3.1 (95%CI: 1.8-5.4) **Compliance (ADJ OR 95% CI)** Inadequate health insurance 83.8 % OR=1.4 (95%CI: 0.57-3.6) Household income (US $) 35,000: 84.8% REF 35,000-74,999: 79.4% OR=0.87 (95%CI: 0.47-1.6) 75,000+: 77.9% OR=0.89(95%CI: 0.42-1.9)	**V** Differential rates of CRC testing are related to differences in both physician recommendation of tests and patient compliance with recommendation, and are associated with a variety of patient characteristics. Physicians should be consistent in recommending and encouraging all adults age 50 and older to undergo timely CRC testing. In making these recommendations, physicians should be aware that some groups may be less likely to adhere than others.

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[3] HMO member: commercial, Medicare, Medicaid health insurance.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					HMO member : 80.7% OR=1.2 (95%CI: 0.74-2.1) Have primary doctor : 81.4% OR=1.7 (95%CI: 0.72-4.0) **Testing (ADJ OR 95% CI)** Inadequate health insurance: 49.2% OR=0.64 (95%CI: 0.38-1.1) Household income (US $) 35,000: 59.7% REF 35,000-74,999: 58.5% OR=1.3 (95%CI: 0.86-2.0) 75,000+: 65.3% OR=2.0(95%CI: 1.2-3.5) HMO member: 64.2% OR=1.5 (95%CI: 1.0-2.1) Have primary doctor: 62.8% OR=2.9 (95%CI: 1.6-5.0) Race and education were not associated with recommendation, compliance or testing	

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Woodrow C., 2006	To examine GPs' attitudes and information needs with regard to bowel cancer screening, with a view to developing an information pack for primary care teams that will be circulated prior to the introduction of the programme. Cross-sectional survey (qualitative study) England	Random sample of GPs participating or not participating in the pilot phase of Bowel Cancer Screening Programme (N=32). Telephone interview about attitudes towards the introduction of the Bowel Cancer Screening Programme, expected or actual increases in workload, confidence in promoting informed choice, and preferences for receiving information about the programme.	Bowel cancer screening Pilot GP vs Non-pilot GP	Attitudes of GP about bowel cancer screening.	Positive <u>attitudes</u> for the introduction of a national screening for bowel cancer by many of the pilot and non-pilot GPs. <u>Reservations</u> of non pilot GPs about welfare, participation and increased workload. Pilot Gps reported holding similar reservations prior to their involvement in the programme. A few GP indicated that they currently felt able to promote informed choice in patients who consulted them about taking part in screening. The majority of GP needed additional information (risks and benefits of screening, statistical information about the screening programme, evidence of detection and survival rates) in order to be able to achieve this.	**V** The study has found considerable GP support for the introduction of the new Bowel Cancer Screening Programme. Nonetheless, GPs hold some significant reservations regarding the programme. It is important that the information needs of GPs and other members of the primary care team are addressed prior to the roll-out of the programme so they are equipped to promote informed choice and provide support to patients who consult them with queries regarding screening.

Author, publication year	Intervention	Study Objective Study design	Participants	Outcome	Results	Level of evidence Conclusions
Seifert B, 2008	Implementation of national CRC screening programme (FOBT/colonoscopy) in the Czech Republic in 2000	To share the experience from the Czech national CRC screening programme, established in 2000. Time series analysis Czech Republic	About 1.75 million of women and men aged over 50 years and clients of GHIF (General health Insurance Fund).	Compliance	**Number of FOBTs performed in general practice** Year 1999: 8500 Year 2000: 13716 Year 2001:139575 Year 2002: 188971 Year 2003: 207636 Year 2004:232930 Year 2005: 239795 **Number of colonoscopies from FOBTs-positive** Year 2000: 827 Year 2001: 7286 Year 2002: 9184 Year 2003: 9530 Year 2004: 10481 Year 2005: 10143 **Number of total colonoscopies in GHIF client** Year 2000: 58425 Year 2001: 61611 Year 2002: 71090 Year 2003: 76812 Year 2004: 85204 Year 2005: 87991	**IV** CRC screening is experiencing a rapid expansion and effective programmes are now available. GPs should play a substantial role in CRC screening either by assessing the risk of their patients, explaining the screening options, or by deciding on the most individually-appropriate strategy within their local health care system. Implications of the population based screening for primary care should be considered and further studied.

Methodological quality; the intervention occurred at a clearly defined point in time; less than 3 data points recorded before and 3 or more data points recorded after the intervention; the intervention was independent from other changes; the intervention itself was unlikely to affect data collection; the outcome variables are objective; completeness of data set

2.6   Active invitation of non-attenders

2.6.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 7

Is active invitation of not yet covered asymptomatic people eligible for colorectal cancer screening effective and cost effective in improving coverage, equity in access?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older not yet undergone to colorectal cancer screening test (if scientific literature about colorectal cancer screening is not available other condition as breast cancer or cervical cancer can be searched)
I: Active invitation to screening (letters, appointment, telephone call etc - GP's involvement)
C: Different strategies
O: Increase in Coverage, Equity: no difference in covered population for social class or socio-economic level, cost-effectiveness
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, Interrupted time series analysis, feasibility studies

SEARCH METHOD

We weren't able to define a search strategy by key-words or mesh terms specific enough to retrieve an affordable number of references because of the lack of specific mesh terms for this topic in the databases. We hand-searched references quoted into the IARC Handbooks of Cancer Prevention "Cervix Cancer Screening" (1). We therefore used the function "related articles" with the articles specific on this topic.

RESULTS

No articles about colorectal cancer were found. We found three RCTs: two about cervical cytology screening (2, 3) and one about mammography screening (4).
The first study about cervical cytology screening explored the effect of including a fixed appointment in the letter versus an open invitation to make an appointment in women not yet undergone to a smear: compliance was significant higher for women inviting with a fixed appointment (47% vs 32%). The other one evaluated the effectiveness of three methods of providing health education on the uptake of cervical smear test versus no intervention among 737 Asian women not yet undergone to a smear. The face-to-face approach (home visits with delivering educational material through video or leaflet and fact sheet) seemed to be more effective than sending the same materials with an advising letter for a cervical smear test by post (30% and 26% vs 11%).

The study about mammography explored the effectiveness and cost-effectiveness of motivational intervention with nurse prompt for a mammogram appointment plus counselling for physicians, pamphlet and reminder call before mammogram appointment versus no intervention in women non compliant with mammography screening. The motivational intervention seems effective, with more than twice the percentage of intervention women receiving mammograms compared with the control women (49% vs 22%) but the results of statistical significance test was not reported. The cost effectiveness was measured at $559 per additional woman who received a mammogram as a result of this intervention.

CONCLUSIONS

No firm conclusions can be drawn because no studies were found on population not attending colorectal cancer screening. Indirect evidence derived from three small RCTs on women not attending mammography or pap test screening show that invitation scheme with a letter send with a specific appointment is more effective than letter sent with an open invitation. The involvement of nurse and physicians can be very effective in improving compliance while the personal contact with a research assistant for a health education seemed to increase screening uptake in relation to an invitation by post. (LEVEL OF EVIDENCE II).

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2.6.2 Evidence tables

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Wilson A., 1987	To discover whether a letter of invitation from the general practitioner to women with no record of having had a cervical smear test would be more effective if it contained a definite date and time for a smear test than if it just invited the woman to contact the surgery and make her own arrangements. RCT UK	250 women aged 45-65 years with no record of having had a cervical smear. Women were patients of five general practices and living in a geographic area without established cervical cytology programme. Women were randomised to receive two different invitation strategies: letter only group and appointment group.	Invitation letter for cervical cytology screening: <u>Letter only group</u>: letter inviting the patient to contact the surgery to make arrangements for a smear test (n=125); <u>Appointment group:</u> a letter that included an appointment for a smear and asked the patient to make alternative arrangements with the surgery if it was inconvenient or if she wished to cancel for other reasons (n=125)	compliance	<u>Compliance after initial letter , n (%)</u> Letter only group: (21%) Appointment group: (36%) % Greater response shown by appointment group (95%CI): 15% (4%-27%) <u>Cumulative total after first reminder, n (%)</u> Letter only group: (28%) Appointment group: (44%) % Greater response shown by appointment group (95%CI): 16% (4%-28%) <u>Cumulative total after second reminder, n (%)</u> Letter only group: (32%) Appointment group: (47%) % Greater response shown by appointment group (95%CI): 15% (3%-28%) <u>Cumulative total women aged 45-54 after second reminder, n (%)</u> Letter only group: (38%) Appointment group: (48%) % Greater response shown by appointment group (95%CI): 10% (-7%-26%) <u>Cumulative total women aged 55-65 after second reminder, n (%)</u> Letter only group: (23%) Appointment group: (47%) % Greater response shown by appointment group (95%CI): 24% (6%-43%)	**II** Our results suggest, however, that middle aged women who have not had a smear test are more likely to accept an invitation to have one if the general practitioner offers a specific appointment rather than an open invitation. This was especially true for women aged 54-65.

Quality assessment: unit of allocation: patient; unit of analysis: patient; allocation concealment: adequate; performance bias: no blinding; protection against contamination: it is likely that the control received the intervention; attrition bias: 10 loss to follow up (3 because left their practice and 7 because their letter returned as "address unknown"; 3 loss from letter only group and 7 loss from appointment group); detection bias: blinding of outcome assessor: no

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
McAvoy BR, 1991	To determine the effectiveness of three different methods of providing health education on the uptake of cervical smear tests among a random sample of Asian women in Leicester who had never had a smear test. RCT Leicester	737 Asian women lived in Leicester who were not recorded as ever having had a cervical smear test. Patients were randomised to receive different method of providing health education: visited and video group (group A), visited and leaflet group (group B), leaflet and fact sheet by post group (group C) and not contacted at all group (group D).	Health education intervention through: A: the home visit of a research assistant who showed a video of a series of simple questions and answers concerning the cervical smear test accompanied by appropriate images and graphics. Administered questionnaire and fact sheet at the end for all women (n=263) B: the home visit of a research assistant who showed a leaflet which describes in strip cartoon format the cytotest. Administered questionnaire and fact sheet at the end for all women (n=219). C: leaflet and fact sheet by post in the appropriate language together with a covering letter advising attendance for a cervical smear test if one had not been taken before (n=131) D: no intervention (n=124)	Compliance (cervical smear test recorded on computer) within four months after intervention	**Compliance, n(%)** D (5%) vs C (11%) CI= (-2.3%,14.1%) A (30%) vs B (26%) CI 95%= −3.6% - 12.4% B vs C B 26% C: 11% 95%CI= (5.5%, 25.1%) A vs C A: 30%, B: 26% 95%CI= (10.8%, 28.7 %) Difference among group A, B, C and D: X^2=44.8, df=3; p<0.0001 No significant correlation between uptake of smear testing and age, education or religion.	**II** Health education interventions increased the uptake of cervical cytology among Asian women in Leicester who had never been tested. Personal visits were most effective irrespective of the health education materials used, but there was some evidence that home viewed videos may be particularly effective in one of the most hard to reach groups: Urdu speaking, Pakistani Moslems. Written translated materials sent by post were ineffective.

Quality assessment: allocation concealment: unclear; performance bias: no blinding; protection against contamination: it is unlikely that the control received the intervention; attrition bias: 159 (93 from group A and 66 from group B) lost because not contactable or not agreed to participate; detection bias: blinding of outcome assessor: unclear.

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Thompson B., 2002	To explore the effectiveness and cost-effectiveness of promoting mammography among women using inner city public health hospital as their major health provider. RCT USA	231 women aged 50-74 years, enrolled in a public health hospital clinic, noncompliant with mammography screening and had a routine clinic appointment during the study period (15 months). Patients were randomised to receive motivational intervention (intervention group=149) or usual care (control group=82).	Motivational intervention to increase mammography rates with: Intervention group: mammography counselling for physicians, nurse prompt for a mammogram appointment, use of audiovisual and printed patient education materials, transportation assistance in the form of bus passes, reminder call before mammogram appointment (n=149) Control group: usual care and no extra activities (n=82) Intention to treat group: eligible women for the intervention whether they received it or not (n=196)	Compliance within 8 weeks of the index clinic visit; cost effectiveness	**Compliance** *(within 8 weeks of index visit)* Intervention 73 (49%) Control 18 (22%) Intention to treat 73 (37%) Test for statistical significance not reported **Total cost of intervention women screened** Intervention $22507 Control $0 Intention to treat $23731 **Cost per woman** Intervention $151 Control $0 Intention to treat $122 **Cost per additional woman screened** Intervention $559 Control $0 Intention to treat $813	**II** The motivational intervention was effective, with more than twice the percentage of intervention women receiving mammograms compared with the control women. This project demonstrated that women could be motivated to receive mammograms at relatively low cost. The cost model used here provides a useful tool for clinics to use in deciding whether to implement new programs.

Quality assessment: allocation concealment: adequate; performance bias: no blinding; protection against contamination: it is unlikely that the control received the intervention; attrition bias: lost to follow up not reported; detection bias: blinding of outcome assessor not relevant because objective outcome has been used.

2.7 Eligibility – family history

2.7.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 8

Which characteristics of family history for colorectal cancer are necessary to assign people to screening protocols different from the strategy adopted for average risk populations?

PICOS

P: Subjects with family history of colorectal cancer
I: Screening protocols
C: Not applicable
O: Detection rate of advanced lesions, Interval cancers , Site distribution of lesions
S: (Systematic reviews of) cohort studies, case control studies

SEARCH METHOD

In the first instance systematic reviews have been searched. We searched also primary studies published since 2000.

Search strategy

PubMed: "Mass Screening"[Mesh] AND "Colorectal Neoplasms"[Mesh] AND (("family"[MeSH Terms] OR family[Text Word]) AND ("history"[Subheading] OR "history"[MeSH Terms] OR history[Text Word]))

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED
Embase: mass screening.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] AND Colorectal Neoplasms AND (family history.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] OR first degree relative.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] OR pedigree.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw].

RESULTS

With the bibliographic search we retrieved 14 studies. 8 studies fulfilled the inclusions criteria and were included in our review.

We found one systematic review published in 2001 (8), 4 case control studies (1,2,4,7) one prospective cohort studies (5) and 2 cross-sectional studies (3,6).

All studies assessed the risk of colorectal cancer in subjects with family risk of colorectal cancer.

The systematic review included 20 case control studies and 7 cohort studies reporting the risk of CRC in relatives of patients with CRC and 9 case control studies reporting the risk of CRC in relatives of patients with adenomas published until 1999 (171,079 participants). The methodological quality of the

review was not very good: only one database has been searched (MedLine), it is not specified if a language restriction was used; **Quality assessment** of primary studies has not been done, it is not specified if more than one author independently assessed studies for inclusion and extracted data, there is no description of number and reason of excluded studies. The review combined through meta-analysis case control studies and prospective cohort studies altogether. The review found that individuals with family history of colorectal cancer have a significant increased risk of developing CRC. Risk are greater for relatives of patients diagnosed young (less than 59 years), those with two or more affected relatives and relatives of patients with colonic cancer.

Two case control study (1,7) assessed the risk of CRC of first degree relatives of patients with large adenomas. One (7) included 168 relatives and 307 matched controls. It found that risk of colorectal cancer is slightly increased in first degree relative of patients with large adenomas. Authors suggest that these relatives should monitored as carefully as relatives of patients with colorectal cancer. The other study (1) included 208 subjects with large adenomas and 154 subjects with small adenomas,635 polyps or cancer free controls. It found an increase of risk of cancer. Also the systematic review (8) included 9 case control studies assessing this risk and found the same results. 1 case control studies (1), 1.168 participants, assessed the risk of CRC in first degree relatives of patients with CRC. The study found an association with an increased risk of CRC. Risk is greater for relatives diagnosed with cancer at young age (less than 64 years).

One case control study (4), 448 participants aged 40-50 years , assessed the risk of adenomas in first degree relatives of patients with colorectal cancer. It found a significant higher prevalence of adenomas .

One case control study (2) assessed the utility of using a scoring system which reflects the severity of familial risk. It includes 992 participants. The scoring system proposed is the following: each first degree relative with CRC: 3 points; Each 2nd degree relative with CRC: 1 point; Families with one or more 1st degree relative <50 years extra 3 points; families with one or more 2st degree relative <50 years extra 1 point; families with multiple relatives on same side of family: extra 3 points. Patients are classified as a low risk if they have 1-4 points, at medium risk if they have 5-7 points, at high risk if they have 8-10 points, at very high risk if they have more than 10 points. The study found that in the two categories system proposed for quantifying familial risk patients having less than 8 point are at low risk and patients having more than 8 points are at high risk. Surveillance protocols could be designed through use of these categories.

The methodological quality of case control studies is as follows: 2 studies adjusted for potential confounding (4,7); all but one (1) included a consecutive series of cases; all studies used the same method of ascertainment of exposure and outcome for cases and controls. All but one study (2), which used secure records, ascertained exposure by interview All but one study (4) selected controls from the same source of cases.

Two cross-sectional study (3,6) assessed the association between family history of CRC and prevalence of colorectal cancer. They included 90898 participants from the general population aged 40 years and older. The studies found that family risk of colorectal cancer in first degree relatives is associated with an increased risk of colorectal cancer.

Finally one prospective cohort study (5) followed for 16 year 1143 subject with family history of CRC. 554 of subjects fulfilled the Amsterdam criteria for HNPCC. The are subjects are classified as follows: subjects with at least three relatives affected. One first degree of the other two, no cases <50 years:391; subjects with two first degree , ore one first degree and one second degree, who are first degree relatives of each other: 536; subjects with one first degree <45 years: 197. The study found that all these group could be considered at moderate risk of developing CRC and concluded that colonoscopic screening is not indicated under 45 years in subjects at moderate risk. Surveillance intervals of more than five years may be appropriate in individuals with a moderate risk. The methodological quality of the study is good: the exposed cohort is truly representative of the population with family history of CRC, the ascertainment of exposure is done by clinical records, the

outcome assessment is objective for both the more and less exposed subjects, the computation of risk is done adjusting for major potential confounding.

CONCLUSIONS

All the retrieved primary studies and a systematic review which includes 36 studies show a consistent increased risk of colorectal cancer and adenomas in first degree relatives of patients with CRC. Two studies found also an increased risk in first degree relatives of patients with large adenomas. First degree relatives of patients with CRC not fulfilling the Amsterdam criteria should be considered at moderate risk of cancer. Some authors suggest that these patients should be followed by screening colonoscopy starting not before than 45 years and not more frequently than every five years (LEVEL OF EVIDENCE III-IV)

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2.7.2 Evidence tables

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Benhamiche – Bouvier 2000	first degree relative of patients with colorectal cancer or large adenomas	Case control	Residents in the Cote d'Or area. Aged 30 to 79 between 1985 and 1990. 171 subjects with CRC, 208 subjects with adenoma of 10mm or more, 154 subjects with small adenomas, 426 polyps free controls and 209 general population controls France	Relative risk and Cumulative risk of colorectal cancer in subjects with first degree relatives with colorectal cancer	One affected first degree relative RR: 2.1 (CI95%1.1-3.7) Cumulative risk 0.74 years Male: 8.7% (CI95% 4.9-13.6) Female: 4.9% (CI95%2.7-7.6) One affected first degree relative <45 years RR: 3.7 (CI95%1.5-9.1) Cumulative risk 0.74 years Male: 16.4% (CI95% 6.7-39.4) Female: 9.1% (CI95%3.7-21.9) One affected first degree relative >45 years RR: 1.8 (CI95%1.2-2.9) Cumulative risk 0.74 years Male: 7.7% (CI95% 5.37-11.4) Female: 4.3% (CI95%2.9-6.3) One affected first degree relative with large adenoma RR: 2.1 (CI95%1.3-3.4) Cumulative risk 0.74 years Male: 8.4% (CI95% 5.6-11.9) Female: 4.7% (CI95%3.1-6.6) Two affected first degree relatives RR: 5.7 (CI95%1.7-19.3) Cumulative risk 0.74 years Male: 25.6% (CI95% 7.6-85.3) Female: 14.3% (CI95%4.2-47.4)	IV the risk is high enough to advise a screening colonoscopy after age 40 for first degree relatives of patients with colorectal cancer before age 45 or for those who have at least two affected first degree relatives.

Quality assessment: Adequate definition of the cases with independent validation; potential for selection biases or not stated; Controls selected from the hospital and from the community; No description of source of controls; No adjustment for potential confounders; Exposure ascertained by interview; not specified if the interviewer was blind to case/control condition; Same method of ascertainment for cases and controls; No description of rate of non responders

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Church 2005	first and second degree relative of patients with colorectal cancer	Case control	992 subjects who had a colonoscopy classified with a scoring system which reflects the severity of familial risk: Each first degree relative with CRC: 3 points Each 2nd degree relative with CRC: 1 point Families with one or more 1st degree relative <50 years extra 3 points Families with one or more 2st degree relative <50 years extra 1 point Families with multiple relatives on same side of family: extra 3 points Low risk: 1-4 points Medium risk: 5-7 points High risk: 8-10 points Very high risk: >10 points USA	Prevalence of adenomas, hyperplastic polyps, cancer at colonoscopy	Low risk: 513 subjects Medium risk: 171 subjects High risk: 84 subjects Very high risk: 28 subjects Control (no family history): 196 subjects Mean numbers of adenomas: Control: 0.4 ± 0.8 Low-medium risk: 1.0 ± 2.2 High-very high risk: 1.7 ± 2.7 P<0.0001 Mean number of hyperplastic polyps Control: 0.3 ± 0.8 Low-medium risk: 0.7 ± 1.3 High-very high risk: 0.8 ± 1.4 P=0.003 n. (%) of cancer: Control: 2/196 (1.0%) Low-medium risk: 11/684 (1.6%) High-very high risk: 4/112 (3.6%) OR of one or two adenomas Low-medium risk: 1.73 (CI95%1.19-2.59) High-very high risk: 2.39 (CI95%1.41-4.08) OR of three or more adenomas Low-medium risk: 5.70 (CI95%2.44-13.32) High-very high risk: 10.35(CI95%3.97-26.97)	**IV** In the two categories system proposed for quantifying familial risk patients having less than 8 point are at low risk and patients having more than 8 points are at high risk. Surveillance protocols could be designed through use of these categories.

Quality assessmen: Adequate definition of the cases with independent validation; consecutive or obviously representative series of cases; Control selected from the same databases; No adjustment for potentials confounding; Exposure ascertained by secure records; Same method of ascertainment for cases and controls

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Sandhu 2001	Family history of first degree relative with colorectal cancer	Cross-sectional survey	General population aged 45-74 identified from list of general practices willing to participate at the study. N: 30353, 2069 of which with family history UK	Prevalence of colorectal cancer	Adjusted OR of colorectal cancer (adjusted for: age, smoking history, BMI, education Family history OR 2.32 (CI95% 1.43-3.76) 1 affected first degree relative OR:2.11(CI95% 1.26-3.54) ≥2 affected first degree relative OR:5.29 (CI95% 1.63-17.17) Age first degree relative at diagnosis ≥65 OR 1.42 (CI95% 0.66-3.08) 45-64 OR 3.26 (CI95% 1.57-6.75) <45 OR 4.93 (CI95% 1.17-20.70)	**IV** Family risk of colorectal cancer in first degree relatives is associated with an increased risk of colorectal cancer.

Author, publicatio n year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Menges 2006	Family history of first degree relative with colorectal cancer	Case control	First degree relatives of patients with CRC identified by the cancer registry aged 40-50 years N:448 Germany	Prevalence of adenomas , histological type and location	Adjusted OR for Polypoid lesions: 2.48 (CI95%1.60-3.84) Hyperplastic polyps :1.56 (CI95%0.90-2.68) Adenomas : 3.02 (CI95%1.65-5.51) High risk adenomas: 2.56 (CI95%0.87-7.47) Location of adenomas: Proximal to sigmoid colon Family history: 52% Controls: 29%	**IV** First degree relatives of patients with CRC aged 40-50 years have a significant higher prevalence of adenomas than controls, with a tendency towards a more proximal location. These data support a screening colonoscopy in first degree relatives between 40 and 50 years

Quality assessment: Adequate definition of the cases with independent validation; consecutive or obviously representative series of cases; Control selected from the general population; adjustment for major potentials confounding (age and gender); Exposure ascertained by standardized questionnaire;; Same method of ascertainment for cases and controls; No description of rate of non responders

Author, publication year	Condition	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Dove-Edwin 2005	Subjects with family history of colorectal cancer	Prospective cohort study	Families registered at the St Mark's Hospital Cancer Research family cancer clinic. Patients received colonoscopy every five years or every three if an adenoma was detected N:1678 UK	16 years	Incidence of single simple adenomas , multiple simple adenomas, metaplastic polyps, high risk adenomas, cancer	1143 subjects had at least two colonoscopies 1. Subjects fulfilling the Amsterdam Criteria: 554 2. Subjects with at least three relatives affected. One first degree of the other two, no cases <50 years:391 3. subjects with two first degree , ore one first degree and one second degree, who are first degree relatives of each other: 536 4. subjects with one first degree <45 years: 197. Median age at first colonoscopy: 41 years Adjusted proportions of high risk adenomas and cancer: Group 1: 5% and 1% Group 2-4:1.7% and 0.1% Adjusted proportions of advanced neoplasia <50 years: Group 1.4.6% Group 2.:0.4% Group 3:0.5% Group 4: 2.2%	III Colonoscopic surveillance is effective in preventing CRC in individuals with HNPCC and in individuals with family history of CRC not meeting the Amsterdam Criteria. Colonoscopic screening is not indicated under 45 years in subjects at moderate risk (group 2-4). Surveillance intervals of more than five years may be appropriate in individuals with a moderate risk (group 2-4)

Quality assessment: Exposed cohort truly representative of the population with family history of CRC; Lack of non exposed cohort (general population at average risk); Ascertainment of exposure by clinical records; The outcome of interest was present at the start of the study for some patients but analysis adjusted for it; Adjustment for major potentials confounding (age and gender and family history); Assessment of outcome objective for more exposed and less exposed; More that 5% of subjects lost at follow up. No description provided of lost subjects

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Nakama 2000	Family history of first degree relative with colorectal cancer	Cross-sectional survey	General population sample aged 40 and older participating to a FOBT screening and sample of workers participating to a colonoscopy screening.. N: sample with FOBT: 59406. Sample with colonoscopy: 6139. Subjects divided in two group: 1. with family history for CRC 2. without family history of CRC on a basis of self completed questionnaire Japan	Prevalence of positive FOBT Prevalence of colorectal cancer	FOBT group 53.212 subjects without family history 6194 with family history Positivity rate of FOBT No family history: 5,4% Family history: 8.1% P:<0.01 Cancer detected: No family history: 78/2888 (PPV:2.7%) Family history: 35/505 (PPV 6.9%) P:<0.05 Detection rate of CRC: No family history: 0.15% (CI95%0.12-0.18) Family history: 0.57% (CI05%0.38-0.76) P:<0.05 Colonoscopy group: 5491 subjects without family history 648 with family history Detection rate: No family history: 29/5491: 0.53%(CI95%0.34-0.72) Family history: 15/648: 2.3% (CI95%1.15-3.47)	**V** Family risk of colorectal cancer in first degree relatives is associated with an increased risk of colorectal cancer.

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Cottet 2007	First degree relative of patients with large adenomas	Case control	First degree relatives of patients with large adenomas and controls without family history recruited in 18 gastroenterology units aged 40-75 years N: 168 relatives, 307 matched control France	Risk of colorectal neoplasia	Any neoplasia Relatives: 22.6% Controls:16.3% Adjusted OR: 1.56 (CI)%%0.96-2.53) Distal neoplasia: Relatives: 16.8% Controls:11.4% Adjusted OR: 1.66 (CI95%0.95-2.91) Proximal neoplasia Relatives: 6% Controls:6.2% Adjusted OR: 1.14 (CI9%5 0.51-2.58) High risk adenomas: Relatives: 7.2% Controls:4.2% Adjusted OR: 1.80 (CI95%0.78-4.13) Cancer or large adenomas Relatives: 8.4% Controls:4.2% Adjusted OR: 2.27 (CI95%1.01-5.09) Relatives of index case younger than 60 years: Adjusted OR: 3.82 (CI95%0.92-15.87)	**IV** Risk of colorectal cancer is slightly increased in first degree relative of patients with large adenomas. Authors suggest that these relatives should monitored as carefully as relatives of patients with colorectal cancer.

Quality assessment: definition of the cases by face to face interview with patients with large adenomas to identify relatives; consecutive or obviously representative series of cases; Control selected from the same databases; adjustment for major potentials confounding (age, sex geographical area); Exposure ascertained by interview; not specified if the interviewer was blind to case/control condition; Same method of ascertainment for cases and controls; non responders rates described

Author, publication year	Condition	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Johns 2001	First degree relative of patients with CRC and adenomas	Systematic review	Twenty case control studies and seven cohort studies reporting the risk of CRC in relatives of patients with CRC Nine case control studies reporting the risk of CRC in relatives of patients with adenomas	Risk of colorectal neoplasia	RR of CRC for subjects with at least one first degree relative with CRC: 26 studies RR 2.25 (CI95%2.00-2.53); there was a significant heterogeneity RR if relative had a colon cancer:11 studies RR:2.42 (CI95%2.20-2.65) RR if relative had a rectal cancer: 11 studies RR: 1.89 (CI95%1.62-2.21) RR of right sided colon cancer: 9 studies RR:2.25 (CI95%1.96-2.59) RR of left sided colon cancer: 9 studies RR: 2.27 (CI95%1.95-2.63) RR of CRC for subjects with first degree relative with adenoma: 9 studies RR: 1.99 (CI95% 1.55-2.55) RR of CRC for subjects with more than one first relative with CRC: six studies RR:4.25 (CI95% 3.01-6.02) RR of CRC for subjects with relatives diagnosed with CRC before 45 years: 5 studies RR: 3.87 (CI95% 2.40-6.22) RR of CRC for subjects with relatives diagnosed with CRC between 45 and 59 years: 5 studies RR: 2.25 (CI95% 1.85-2.72) RR of CRC for subjects with relatives diagnosed with CRC >59 years: 3 studies RR: 1.82 (CI95% 1.47-2.25)	**IV** individuals with family history of colorectal cancer have a significant increased risk of developing CRC. Risk are greater for relatives of patients diagnosed young, those with two or more affected relatives and relatives of patients with colonic cancer.

SR Johns 2001

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE (1966-1999), SEARCH OF REFERENCES OF RETRIEVED STUDIES
	Date restriction	Up to December 1999
	any restriction	Not specified
Selection	Inclusion and exclusion criteria	Studies that reported familial risks of CRC in first degree relatives
Validity assessment	Criteria and process used	Validity assessment of primary studies not perfomed
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	RR computed by a random effect model
Results Trial flows	Trial flow and reason for exclusion	NO
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

2.8   Diagnostic assessment

2.8.1   Summary document

CLINICAL QUESTION 9

Is active invitation to diagnostic assessment more effective than spontaneous presentation in improveing the proportion of positives undergoing necessary assessment?

CLINICAL QUESTION 10

Which strategy to invite positive patients to undergo diagnostic assessment is more effective in improving detection rate and the proportion of positives undergoing necessary assessment?

PICOS (FOR BOTH)

P: Patients with positive results
I: Active invitation to diagnostic assessment. Strategy to invite positive patients to diagnostic assessment (nurse counselling, fixed appointment)
C: Spontaneous presentation
O: Proportion of positives undergoing diagnostic assessment. Detection rate. Cost effectiveness
S: (systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, feasibility studies

CLINICAL QUESTION 11

Are strategies aiming to solicit positive patients who are non responders to diagnostic assessment effective and cost effective in improving compliance with further investigations, detection rate?

PICOS

P: Positive patients non responders to diagnostic assessment
I: Strategy to solicit non-responders to undergo diagnostic assessment (invitation letter, nurse counselling)
C: No intervention
O: Proportion of non-responders who underwent diagnostic assessment
Proportion of cases (adenomas, cancers) detected among non-responders. Cost effectiveness
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, interrupted time-series, feasibility studies

SEARCH METHOD

We weren't able to define a search strategy by key-words or mesh terms specific enough to retrieve an appreciable number of references because of the lack of specific mesh terms for this topic in the databases.

We contacted experts in the field to retrieve published articles on this topic who suggested three articles (1, 2, 3). We therefore used the function "related articles" with suggested articles.

No relevant articles were identified.

RESULTS

Three RCTs were retrieved for these questions (1, 2, 3).

Myers et al. 2001, 2004 (1, 2) evaluated the impact of a physician-directed intervention (reminder-feedback for physician and educational outreach intervention) aimed to increase the recommendation to patients of FOBT positives to perform a Complete Diagnostic Examination and on complete diagnostic evaluation (CDE) rates in primary care practices versus the traditional screening program in 2,992 screening FOBT+ patients. The reminder-feedback plus educational outreach intervention significantly increased CDE recommendation (OR (I vs C) = 2.28; 95% CI: 1.37, 3.78) and performance (OR (I vs C) = 1.63; 95% CI: 1.06, 2.50).

Stern et al. 2000 (3), conduced a randomised trail to assess the feasibility of converting FS to CT in patients with abnormal screening FS in a single visit (conversion) *versus* traditional screening with FS and, where appropriate, CT on a subsequent day (control) in 235 patients invited for a screening sigmoidoscopy. The conversion strategy leads to similar clinical outcomes compared to traditional screening: there were found no carcinoma both in control and conversion groups; the difference in the proportion of proximal adenomas by CT (control 8 (27%) vs conversion 12 (41%)) was not significant. Compliance for the conversion group was higher: three patients (9%) with abnormal sigmoidoscopy in the control group didn't return for CT.

CONCLUSIONS

Only two studies assessing different kind of intervention to increase diagnostic work up for FOBT positive patients were retrieved. The reminder-feedback plus educational outreach intervention for physicians increased CDE recommendation and performance rate in relation to the standard screening program in patients with abnormal faecal occult blood testing (FOBT). The immediate conversion (in a single visit) from FS to CT in patients with abnormal screening sigmoidoscopy (a polyp >5mm or multiple diminutive polyps) led to similar clinical outcomes (proximal adenomas and cancers detected) compared to traditional screening while improving compliance with colonoscopy (LEVEL OF EVIDENCE II).

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2.8.2 Evidence tables

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Myers R.E., 2004 Myers R.E., 2001	To evaluate the impact of a physician intervention on the recommendation of CDE[4] to patients and performance rates of CDE in primary care practices. Randomised controlled trial USA	318 practices (with 470 PCPs surveyed and 168 unsurveyed PCPs) were randomised to receive the screening program and combined CDE reminder-feedback and educational outreach intervention (intervention group) or only the screening program (control group). 2992 screening FOBT+ patients (1798 from control group and 1194 from intervention group) aged 50 and older were included. No significant difference between control and intervention group with regard to gender, race, median years in medical practice and physician background and experience.	Physician-oriented intervention through: (C) Control group: only the screening program (n=198); (I) Intervention group: screening program, reminder-feedback for physician and educational outreach intervention to enhance CDE, (two detailing visits to the practice and a tailored letter and telephone call delivered to PCPs)(n=120)	CDE and performance rate	**CDE's recommendation rates** <u>Before intervention (period 1) % (n)</u> C 68.9 (1050) *vs* I 64.9 (649) OR (I vs C) (95% CI) adjusted by GEE= 0.83 (0.61,1.13) p=0.23 <u>After intervention (period 3) % (n)</u> C 67.3 (309) *vs* I 79.6 (245) OR (I vs C) (95% CI) adjusted by GEE= 1.89 (1.21,2.97) p=0.005 Control group Within group OR (95%CI) Period 1 vs Period 3=0.93 (0.6,1.26) p=0.63 Intervention group Within group OR (95%CI) Period 1 vs Period 3=2.11 (1.41,3.16) p<0.001 <u>Between group baseline-adjusted OR</u> (I vs C) (95% CI)= 2.28 (1.37, 3.78) p=0.002 OR (95%CI) [5]Period 2 and 3 vs Period 1=1.98 (1.29,3.04) p<0.001 **CDE performance rates** <u>Before intervention (period 1) % (n)</u> C 52.6 (1050) *vs* I 50.2 (649) OR (I vs C) (95% CI) adjusted by GEE= 0.91 (0.69,1.20) p=0.50	**II** The reminder-feedback plus educational outreach intervention significantly increased CDE recommendation and performance. It is notable that the magnitude of the intervention impact was greater for CDE recommendation than CDE performance. This effect probably reflects the impact of the intervention directly on physician behavior (i.e., recommending complete follow up). CDE performance, however, involves patient compliance with the physician recommendation. The intervention did not include patient contact outside of the physician-patient relationship.

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[4] CDE: complete diagnostic evaluation (i.e. colonoscopy or combined flexible sigmoidoscopy plus barium enema X-ray)
[5] Period 2: intervention overlap timeframe

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					<u>After intervention (period 3) % (n)</u> C 53.7 (309) *vs* I 63.3 (245) OR (I vs C) (95% CI) adjusted by GEE= 1.48 (1.04,2.11) p=0.03 <u>Control group</u> Within group OR (95%CI) Period 1 vs Period 3=1.05 (0.81,1.36) p=0.73 <u>Intervention group</u> Within group OR (95%CI) Period 1 vs Period 3=1.71 (1.21,2.40) p=0.03 <u>Between group baseline-adjusted OR</u> (I vs C) (95% CI)= 1.63 (1.06, 2.50) p=0.03 OR (95%CI) Period 2 and 3 vs Period 1=1.22 (0.89,1.77) p ns	

Quality assessment: allocation concealment: adeguate; blindness of provider: no; blindness of practices: no, blindness of PCPs: no; blindness of outcome assessor: no; none lost at follow-up

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Stern M.A., 2000	To assess the feasibility as well as technical and clinical outcomes of converting sigmoidoscopy to colonoscopy in selected patients in a single visit *versus* traditional screening with sigmoidoscopy and, where appropriate, colonoscopy on a subsequent day. RCT USA	235 (227 men and 8 women aged 50 years and older) consecutive patients referred for CRC screening with sigmoidoscopy were randomised to schedule for colonoscopy on a future day after sigmoidoscopy if abnormal screening sigmoidoscopy (control group)or to converte from sigmoidoscopy to colonoscopy in a single visit if abnormal screening sigmoidoscopy (conversion group). No significant difference between control and conversion group with regard to gender, age and race.	Screening sigmoidoscopy followed by: Control group: colonoscopy within 30 days of the FS (patients notified by phone and in writing) if a polyp of >5mm in diameter or multiple diminutive polyps resulted adenomatous after cold biopsy or by a second sigmoidoscopy after 5 years if the first resulted normal (n=121); Conversion group: colonoscopy in the same visit if a polyp of >5mm in diameter or multiple diminutive polyps were seen or by a second sigmoidoscopy after 5 years if the first resulted normal (n=114)	Proportion of positive undergoing to FS, proximal adenomas by CT, proportion of patients who completed the study, patient assessment, physician assessment	<u>Completed study</u> Control 117/121 *vs* Conversion 105/115 *(p ns)* <u>Adenomas by FS</u> Control (28%) *vs* Conversion (28%) *(p ns)* 3 patient (9%) from control group didn't return for colonoscopy. <u>Proximal adenomas by colonoscopy</u> Control (27%) *vs* Conversion (41%) *(p ns)* No carcinoma found in control and conversion group. <u>Procedure difficulty as difficult</u> Control (6%) *vs* Conversion (10%) *(p ns)* <u>Patient comfort level as good or excellent</u> Control (73%) *vs* Conversion (66%) *(p ns)* <u>Patient overall satisfaction as good or excellent</u> Control (86%) *vs* Conversion (79%) *(p ns)* <u>Preference for future screening</u> 96% chose the conversion strategy (n=222 p=0.001)	**II** The conversion strategy is technically feasible and leads to similar clinical outcomes compared to traditional screening while improving compliance with colonoscopy in patients with abnormal sigmoidoscopy.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no, blindness of endoscopist: no; blindness of outcome assessor: no; 4 patients lost (1 refused to participate at the study, 3 didn't return for CT) from control group and 9 lost (1 refused after information about protocol, six didn't bring a driver to the appointment, 2 excluded because protocol mistake of the endoscopist) from conversion group.

2.9 Testing and diagnosis protocols – dietary restriction for FOBT

2.9.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 12

Does dietary restriction needed to perform guaiac FOBT or multiple sampling reduce participation compared to FOBtesting which does not need any restriction?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older
I: Dietary restriction to perform FOBtest; multiple test
C: No dietary restriction, single test
O: Participation
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, interrupted time series, feasibility studies

SEARCH METHOD

In first instance systematic reviews have been searched. We searched also primary studies published since 2000.

Search strategy

MedLine: search 1:"Occult Blood"[Mesh] AND "Patient Compliance"[Mesh] AND "Mass screening"[Mesh]. Search 2: "Mass Screening"[Mesh] AND "Colorectal Neoplasms"[Mesh] AND "Diet"[Mesh] AND "Occult Blood"[Mesh] 1:9, 2:2

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED
mass screening.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] AND occult blood
Embase : exp Colon Tumour/ AND exp Cancer Screening/ AND exp Occult Blood/ AND diet$ restrict$
17

RESULTS

With the bibliographic search we found in MedLine 11 Results. We found in Embase 21 Results. After duplicates were removed there were 28 results in total.

After inspection of titles and abstracts 9 articles were retrieved in full text for further evaluation. 5 fulfilled the inclusion criteria and have been included in the review.

We found one systematic review published in 2001 and 4 RCTs. The systematic review (1) included 5 RCTs with 10,359 participants comparing the FOBT test performed using the Guaiac test with and without dietary restriction. The review is of good methodological quality: it respects all the methodological criteria apart the one concerning the quality evaluation of primary studies included, which has not been done. Authors did not performed a meta-analysis because of the high heterogeneity among trials. Only one of the included trials found a significant difference in compliance in favour of test without dietary restriction; in this trial the dietary restriction was particularly extensive. Authors concluded that advice to patients to restrict their diet and avoid NSAIDs and vitamin C does not substantially reduce completion rate of FOBT, except perhaps when the dietary restriction is particularly extensive.

Methodological quality of primary studies: the allocation concealment was inadequate in one study, unclear in another study and adequate in the others. Contamination was unlikely in one study and unclear in the others. The items relating performance bias and attrition bias were non applicable because the examinations were different (Guaiac vs immunochemical) and the participation rate was the primary outcome in all the studies. Avoidance of detection bias was not feasible in three studies because the examinations were different (Guaiac vs immunochemical) and unclear in the third.

One study (4) compared the participation rate with the immunochemical test with three evacuation collected; one group received instructions for diet restriction and the other did not. Two studies (2,3) compared the participation rate with the Guaiac test with dietary restriction and the immunochemical test without dietary restriction and the last study compared the participation rate between the two tests without dietary restriction in both groups (5). All three RCTs found a significant difference in compliance in favour of the test without dietary restriction. Authors of all the trials concluded that the immunochemical test, which requires only one evacuation collected without dietary restriction could be a better solution to achieve a higher participation rate in the screening for colorectal cancer. (LEVEL OF EVIDENCE I)

REFERENCES

1. Pignone M, Campbell MK, Carr C & Phillips C (2001), Meta-analysis of dietary restriction during fecal occult blood testing, *Eff.Clin.Pract.*, vol. 4, no. 4, pp. 150-156.

2. Federici A, Giorgi RP, Borgia P, Bartolozzi F, Farchi S & Gausticchi G (2005), The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomised controlled trial, *J.Med.Screen.*, vol. 12, no. 2, pp. 83-88.

3. Cole SR, Young GP, Esterman A, Cadd B & Morcom J (2003), A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer, *J.Med.Screen.*, vol. 10, no. 3, pp. 117-122.

4. Cole SR & Young GP (2001), Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer, *Med.J.Aust.*, vol. 175, no. 4, pp. 195-198.

5. van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, Verbeek AL, Jansen JB & Dekker E (2008), Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population, *Gastroenterology*, vol. 135, no. 1, pp. 82-90.

2.9.2   Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusion
Pignone 2001	Dietary restriction during FOBT Control intervention: no dietary restriction	Meta-analysis of Randomised controlled trials (RCT),	5 RCTs. All used guaiac-based Hemoccult test N. of participants: 10.359	Completion rate Positivity rates	Not specified	Completion rates: meta-analysis not performed because of high heterogeneity among trials Hoogwert No restriction:70.5% Restriction: 71.6% Difference: -1.1% (CI95% -3.5%- 1.5%) Elwood: No restriction:20.9% Restriction: 18.1% Difference: 2.8% (CI95% 0%-5) Joseph No restriction:82.2% Restriction: 80.4% Difference: 1.8% (CI95% -3.6%-7.3%) Verne No restriction:52% Restriction: 45.8% Difference: 6.2% (CI95% -1.6%-13.9) Robinson No restriction:72.7% Restriction: 51.3% Difference: 21.4% (CI95% 6.4%-36.4%) Difference in Positivity rates: Meta-analysis of four trial (results of one trial not included in meta-analysis because of heterogeneity of its results): 0% (CI95%-1% - 1%)	I advice to patients to restrict their diet and avoid NSAIDs and vitamin C does not substantially reduce completion rate of FOBT, except perhaps when the dietary restriction is particularly extensive (study by Robinson). Moreover, there was non difference in positivity rate. Moderate dietary restriction is not a major barrier to test completion

SR Pignone 2001

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE (1966-1999), HAND SEARCH OF OTHER REVIEWS AND GUIDELINE
	Date restriction	Up to December 1999
	any restriction	Not specified
Selection	Inclusion and exclusion criteria	Randomised controlled trials (RCT) and quasi RCTs which compared dietary restriction with no restriction on completion rate
Validity assessment	Criteria and process used	Validity assessment of primary studies not perfomed
Data abstraction	Process used	Two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Absolute difference computed by random effect model
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Yes
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes (Meta-analysis performed only for positivity rate, not for completion rate because of high heterogeneity)

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Federici 2005	1. guaiac FOBT test with dietary restriction and three evacuation collected 2. immunochemical FOBT without dietary restriction and one evacuation collected	RCT	Random sample of general practitioner and of their patients GP 130 Patients 7332 Italy	Completion rate	Not specified	Completion rate Guaiac test: 30.4% Immunochemical: 35.5% RR adjusted for provider: 1.20 (CI95%1.02-1.44)	**II** The study showed a 20% higher compliance with the immunochemical test rather than with the Guaiac test.

Quality assessment: avoidance of selection bias: inadequate allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention: reviewers assured verified that cohabitants received the same test; attrition bias: percentage of participants completing the study: the participation rate is the primary outcome; detection bias: blinding of outcome assessor not feasible; intention to treat analysis performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Cole 2003	1.Guaiac (Hemoccult-Sensa) FOBT test with dietary restriction and three evacuations collected 2.FIT test (FlexSure OBT) without dietary restriction and three evacuations collected 3.FIT test (InSure) without dietary restriction and two evacuations collected	RCT	Random sample of general population aged 50-69 years n: 1818 Australia	Percentage of returned test	12 weeks	Percentage of returned test: Hemoccult Sensa: 23.4% FlexSure: 30.5% InSure: 39.6% P<0.00001	**II** The Immunochemical test InSure achieved the best participation rates by simplifying sampling (two evacuation instead of three) and removing the need of dietary restriction

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: unclear: it is possible that communication between experimental and control group could have occurred; attrition bias: percentage of participants completing the study: not applicable: the participation rate is the primary outcome; detection bias: blinding of outcome assessor not feasible; intention to treat analysis performed.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Cole 2001	1. immunochemical test (FlexSure) with dietary restriction and three evacuation collected 2. immunochemical FOBT without dietary restriction and three evacuation collected	RCT	Random sample of general population aged 50-69 years n. 1203 Australia	Participation rate	15 weeks	Participation rate Diet group: 53.3% No-diet group: 65.9% Difference: 12.6% (CI95%7.1%-18.1%)	**II** Dietary restrictions create a barrier to FOBT base screening. The use of immunochemical rather than the guaiac FOBT removes this barier.

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: unclear; attrition bias: percentage of participants completing the study: not applicable: the participation rate is the primary outcome; detection bias: blinding of outcome assessor: not clear; intention to treat analysis performed.

Author, publication year	Study Objective Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Van Rossum L.G., 2008	To randomly compare the test performance parameters of the Hemoccult II G-FOBT (guaiac-based faecal occult blood tests) with the OC-sensor I-FOBT (Immunochemical faecal occult blood tests) in a screening population. RCT The Netherlands	20623 individuals (aged 50-75 years) enlisted from municipal databes and with no symptom were randomised to: G-FOBT group (52.2% of female; 50.4 aged <60 years) or I-FOBT group (51.2% of female; 51.7 aged <60 years) No difference between the FOBT groups regard to age. Gender differences equal for both tests.	CRC screening invitation with information brochure, a consent form, a freepost envelop and one of the following test: G-FOBT= a guaiac-based faecal occult blood test (n=10301) I-FOBT= a immunochemical faecal occult blood test (n=10322) No diet instructions Follow-up examination (colonoscopy) in case of a positive FOBT.	Participation rate	**Participation rate, N (%)** G-FOBT= 4836 (46.9) I-FOBT= 6157 (59.6) Difference= 12.7 (95% CI:11.3-14.1; p<0.01)	**II** Participation and detection rates for advanced adenomas and cancer were significantly higher in the group tested with I-FOBT. By result, 2.5 times more advanced adenomas and cancer and 2.2 times more cancers were detected with I-FOBT compared with G-FOBT. Therefore, G-FOBT significantly underestimates the prevalence of advanced adenomas and cancer compared with I-FOBT in a screening population.

Quality assessment: allocation concealment: adequate; performance bias: blinding of partecipants to the existence of alternative test; protection against contamination: it is likely that the control received the intervention; attrition bias: lost at follow upexamination:14 from G-FOBT and 58 from I-FOBT; detection bias: blinding of outcome assessor not relevant because objective outcome has been used.

2.10 Testing and diagnosis protocols – types of bowel preparation

2.10.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 13

Do different kinds or location of bowel preparation for FS reduce participation?

PICOS

P: General population asymptomatic for colorectal cancer aged 50 years and older
I : Bowel preparation to perform FS: oral vs enema, one vs two enemas, self administered at home vs administered at the screening centre
C: Different kind of bowel preparation
O: Participation
S: (Systematic reviews of) RCTs, cohort studies, Controlled clinical trial, Controlled before and after study, interrupted time series, feasibility studies

SEARCH METHOD

Searches were conducted on MedLine and Embase for papers published in English between 2000 and February 2009.
Search terms:
(((FS AND preparation) OR (sigmoidoscopy AND preparation) OR (FS AND bowel preparation) OR (sigmoidoscopy AND bowel preparation)) AND (oral preparation)) OR (((FS AND preparation) OR (sigmoidoscopy AND preparation) OR (FS AND bowel preparation) OR (sigmoidoscopy AND bowel preparation)) AND (enema preparation)) OR(((FS AND preparation) OR (sigmoidoscopy AND preparation) OR (FS AND bowel preparation) OR (sigmoidoscopy AND bowel preparation)) AND (self administered)) OR (((FS AND preparation) OR (sigmoidoscopy AND preparation) OR (FS AND bowel preparation) OR (((sigmoidoscopy AND bowel preparation)) AND (administered at the centre)) OR (FS AND bowel preparation) OR (sigmoidoscopy AND bowel preparation)) AND (participation))

MedLine
Limits: General population aged 45 years and older; Humans.
The free text search produced 19 results with 2 papers (RCTs) deemed relevant.
Embase
Limits: Humans
The search terms identified 32 papers with 2 papers deemed relevant but included in the Pubmed search.
An other article was suggested by expert in the field (3).

RESULTS:

Three randomised controlled trials were retrieved for this question.

Atkin, 2000 (2) evaluated with a randomised trial the acceptability and efficacy of two methods of self administered bowel preparation (a single phosphate enema and a single sachet of oral sodium picosulphate with magnesium citrate (Picolax) in 1442 patients undergoing screening by flexible sigmoidoscopy. Compliance (attendance and use of allocated preparation at home) with the enema was higher than with the oral Picolax (608 (84%) vs 566 (79%); difference 6%, 95% confidence interval 2% to 10%). Almost half of those who refused oral Picolax used an enema at home (27 (4%); difference -1%, 95% confidence interval -3% to 11%).

Senore 1996 (3) conduced a randomised trail to assess the impact on compliance of three invitation methods, as well as the acceptability and efficacy of two bowel preparation regiments (one enema or two enemas), for sigmoidoscopy screening in 1 170 patients invited to screening by flexible sigmoidoscopy. A total of 278 subjects attended for sigmoidoscopic screening.

The preparation regimen had a marginal influence on the response rate: the estimated overall compliance was 27.8% among subjects allocated to the single enema group and 26.4% among those included in the group receiving two enemas.

We reported the result of the following trial even though outcomes were less pertinent to the question.

Bini, 2000 (1) conduced a randomised trial to compare patient tolerance, quality of preparation, and cost of 2 bowel cleansing regimens (oral or enema preparation) in 250 patients undergoing screening by flexible sigmoidoscopy. Oral preparation consisted of oral bisacodyl followed by 45 mL oral sodium phosphate; enema preparation consisted of oral bisacodyl followed by 2 Fleet enemas.
Patients in the oral preparation group were more likely to complete the bowel cleansing regimen at home than those than in the enema group (100.0% vs. 73.4%, p <0.001).

CONCLUSIONS

Different kinds or location of bowel preparation for FS affect participation in flexible sigmoidoscopy screening: there is a major improvement in compliance of the enema group compared to the oral preparation group (LEVEL OF EVIDENCE II).

REFERENCES

1.   Bini EJ, Unger JS, Rieber JM, Rosenberg J, Trujillo K & Weinshel EH (2000), Prospective, randomised, single-blind comparison of two preparations for screening flexible sigmoidoscopy, *Gastrointest.Endosc.*, vol. 52, no. 2, pp. 218-222.

2.   Atkin WS, Hart A, Edwards R, Cook CF, Wardle J, McIntyre P, Aubrey R, Baron C, Sutton S, Cuzick J, Senapati A & Northover JM (2000), Single blind, randomised trial of efficacy and acceptability of oral picolax versus self administered phosphate enema in bowel preparation for flexible sigmoidoscopy screening, *BMJ*, vol. 320, no. 7248, pp. 1504-1508.

3.   Senore C, Segnan N, Rossini FP, Ferraris R, Cavallero M, Coppola F, Pennazio M & Atkin WS (1996), Screening for colorectal cancer by once only sigmoidoscopy: a feasibility study in Turin, Italy, *J Med.Screen.*, vol. 3, no. 2, pp. 72-78.

2.10.2 Evidence tables

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Bini E.J, 2000	To compare patient tolerance, quality of preparation, and cost of 2 bowel cleansing regimens for flexible sigmoidoscopy. Prospective randomised, single-blind trial USA	250 patients undergoing screening flexible sigmoidoscopy were randomised to receive an oral preparation (group O: male gender 98.4%; mean age 66.4± 9.4) or enema preparation (group E: male gender 98.4%; mean age 66.2± 8.4) No significant difference between the two groups regard to age, gender and race.	Flexible sigmoidoscopy using the following bowel preparations: group O: 10 mg oral bisacodyl (1 h later) followed by 45 mL oral sodium phosphate solution with two 8 ounce glasses of water (n=126) or group E: 10 mg oral bisacodyl followed by 2 Fleet enemas 1 hour before leaving home the morning of the examination (n=124).	Patient tolerance, quality of preparation, nursing preparation time and cost, symptom score, depth of insertion, complications	<u>% patients completing the bowel preparation at home</u> O 100% vs E 73.4% (p<0.001) 33 patients from the group E (19 for inability to administered the enemas without assistance and 14 for fear of having a bowel movement in transit to the hospital) could not complete the preparation at home and took the enemas on arrival to the endoscopy suite. *For the results of the other outcomes see the relative evidence table of the chapter 5 question 4	**II** An oral sodium phosphate preparation in combination with oral bisacodyl results in a superior quality endoscopic examination compared with an enema preparation for patients undergoing screening flexible sigmoidoscopy. This oral prepara tion is better tolerated, results in a more comprehensive endoscopic examination, and is more cost effective. By reducing the discomfort associated with the use of enemas, this oral preparation may improve patient acceptance of flexible sigmoidoscopy as a screening tool for colorectal cancer.

Quality assessment: allocation concealment: inadequate; blindness of provider: no; blindness of patients: yes, blindness of endoscopist: yes; blindness of outcome assessor: yes; None lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Atkin W.S., 2000	To compare the acceptability and efficacy of two methods of self administered bowel preparation for flexible sigmoidoscopy screening: a single phosphate enema and a single sachet of Picolax. single-blind RCT UK	1442 patients (from 2 centres: Welwyn Garden City and Leicester) undergoing screening flexible sigmoidoscopy were randomised to receive an oral laxative (group P) or a sinle phosphate enema (group E). No difference between the two centres for age and gender.	Screening flexible sigmoidoscopy using the following bowel preparations: group E: a single self administered phosphate enema taken 1 h before leaving home for the examination (n=721) or group P: a single sachet of oral sodium picosulphate with magnesium citrate (Picolax) taken at either 2 pm or 6 pm on the day before screening for a morning or afternoon examination respectively and no solid food (n=721). Participants who cancelled their appointment after receiving their bowel preparation were offered an alternative. Patient from group E could have the enema in the unit or Picolax, and patient from group P could have an enema at home or in the unit.	Compliance, acceptability, adverse effects, quality of bowel preparation, complete examinations	**Compliance** Sent bowel preparation (n) E 721 vs P 721 Attended for screening E 94%(676) *vs* P 87% (629) (95%IC difference in %=4 to 10) Attended and used allocated preparation at home E 84%(608) *vs* P 79% (566) (95%IC difference in %=2 to 10) Attended but refused to use allocated preparation at home: E 9%(67) *vs* P 9% (63) (95%IC difference in %=-2 to 4) Used alternative preparation at home E 2%(18) *vs* P 4% (27) (95%IC difference in %=-3 to 1) Used enema in unit E 7%(49) *vs* P 5% (36) (95%IC difference in %=-1 to 4) Attended and used allocated preparation at home (Welwyn Garden City) E 86% (248) *vs* P 79% (237) Attended and used allocated preparation at home (Leicester) E 84% (360) *vs* P 78% (329) No significant difference between the group E and P in the proportions who used an alternative bowel preparation (E 3% vs P 4%) *For the results of the other outcomes see the relative evidence table of the chapter 5 question 4.	II Based on the results of this study, we believe that a single, self administered enema is probably the best available preparation for flexible sigmoidoscopy screening.

Quality assessment: allocation concealment: adequate; blindness of provider: no (yes for consent for randomisation to different bowel preparation); blindness of patients: no, blindness of endoscopist: yes; blindness of outcome assessor: yes; 1 patient (from group E) lost at bowel preparation questionnaire before screening; 59 patients (24 from group E and 35 from group P) lost at questionnaire follow up after test.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Senore C.,1996	To assess the impact on compliance of three invitation methods, as well as the acceptability and efficacy of the bowel preparation regiments, for sigmoidoscopy screening Randomised controlled trial Italy	Number of eligible patients: 1186 Number of enrolled patients:1170 (13 patients because had undergone a colonoscopy within the past 2 years, 3 because severe ill). 1170 (572 males and 598 female aged 55 to 59) patients inviting screening flexible sigmoidoscopy were randomised to receive one of three invitation groups (group A: personal letter, signed by GP, with a pre-fixed appointment; group B: same as for A + letter supporting the study by a well known scientist; group C: letter signed by the study coordinator) and two preparation regimens (group 1: one enema, self administered at home two hours before the test; group 2: two enemas, administered the night before and two hours before the test).	Invitation screening flexible sigmoidoscopy using the following: bowel preparations group 1: one enema, self administered at home two hours before the test (n=587) or group 2: two enemas, administered the night before and two hours before the test (n=583). and invitation procedures: group A: personal letter, signed by GP, with a pre-fixed appointment (n=382) group B: same as for A plus letter supporting the study by a well known scientist (n=381); group C: letter signed by the study coordinator (n=407).	Compliance, quality of preparation, patients'perceptions	<u>Estimated Compliance (%)</u> Group 1 27.8 vs Group 2 26.4	**II** Compliance with this screening procedure tends to be low. One enema, self administered two hours before sigmoidoscopy, can ensure a satisfactory bowel preparation.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no, blindness of endoscopist: yes; blindness of outcome assessor: no; 10 lost at questionnaire follow up; 31 lost patients' perceptions of discomfort; 27 lost at patients' perceptions of embarrassment.

2.11 Additional evidence tables prepared after December 2009

1. Baglietto L, Jenkins MA, Severi G, Giles GG, Bishop DT, Boyle P & Hopper JL (2006), Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer, *J Clin.Epidemiol.*, vol. 59, no. 2, pp. 114-124.

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3. Brenner H, Chang-Claude J, Seiler CM, Sturmer T & Hoffmeister M (2007a), Potential for colorectal cancer prevention of sigmoidoscopy versus colonoscopy: population-based case control study, *Cancer Epidemiol.Biomarkers Prev.*, vol. 16, no. 3, pp. 494-499.

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Author, publication year	Screening test evaluated Comparator test	Study Objective Study design	Study Participants	Outcomes	Results	Conclusion Level of evidence
Baglietto L., 2006	First degree relative of patient with CRC	To review the publications reporting a measure of Familial aggregation of CRC, classify the estimates based on the study design and analytical approach, and estimate the overall type I and type II increased risk by combining the findings of all studies. Systematic review of studies reporting incidence data of familial aggregation	33 articles identified:30 conducted in Europe, 12 in USA, 2 in Canada, 3 in Australia, 2 in Japan and 1 in China. The excess risk due to the presence of affected family members was been presented with a: type I approach (whether disease in the relatives is considered a risk factor for the index person) in 2 cohort studies and in 24 case-control studies; type I approach (whether the disease status of the index person is considered a risk factor for the relative) in 3 cohort studies and in 2case-control studies. 2 studies presented both type I and type II estimates	Type I and type II RR of colorectal cancer	<u>Pooled type I relative risk of CRC associated with having at least one first-degree relative affected:</u> (28 studies): 2.26 (95%CI=1.86-2.73) <u>Estimated RR with the number of affected relatives:</u> from 2.03 for just 1 relative affected (95%CI=1.66-2.49) to 3.95 for 2 or more relatives affected (95%CI=2.49-6.26). No difference in excess risk between males and females (p=0.4). <u>Pooled type I relative risk of colon *vs* rectal associated with having at least one first-degree relative affected:</u> : 2.20 (95%CI=1.95-2.50) *vs*1.79 (95%CI=1.42-2.26) <u>Pooled type I relative risk of CRC associated with having at least one first-degree relative affected:</u> (7studies): 2.81(95%CI=2.05-3.85) <u>RR to sibling *vs* parents</u>: .3.47 (95%CI=2.24-5.40) vs1.85 (95%CI=1.63-2.09)	**III** Having at least one affected first degree relative approximately doubles the risk of developing CRC and the increased risk increases with having more than one affected relative. No difference was observed between males and females, suggesting that the risk factors shared by individuals within a family are not sex-related. The risk associated with having an affected sibling was only slightly higher than the risk associated with having an affected parent. Having a relative with CRC appears to be associated with a greater increased risk of cancer of the colon than cancer of the rectum.

SR– Baglietto 2006

Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	Medline; reference list of retrieved articles;
	Date restriction	From 1966 to 2003
	any restriction	Only English studies
Selection	Inclusion and exclusion criteria	Included Studies: familial risk from incidence data Excluded Studies: familial risk from mortality data alone
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Studies restricted to first degree relatives only.
Quantitative data synthesis	Measures of effect, method of combining results	RR; meta-analysis using fixed and random effect model; test of heterogeneity.
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	no
	summary results	Yes

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Baxter 2009	To evaluate the association between colonoscopy and CRC deaths.. Population based Case control study USA	10 292 case patients aged 52 to 90 years who received a CRC diagnosis from January 1996 to December 2001 and died of CRC by December 2003. and 51 460 matched controls. Each case patient had 5 controls matched for age, sex, income quintile (based on the mean household income of the enumeration area of residence), residence location by health care region during year of diagnosis, Four data source were used to identify cases and controls: The Ontario Cancer Registry, The Ontario Health Insurance Plan database, The Registered Persons Database, The Canadian Institute for Health Information hospital discharge abstract database.	associations between CRC death and colonoscopy performed 6 to 24 months before diagnosis and exposure to any colonoscopy more than 24 months before diagnosis	719 case patients (7.0%) and 5031 controls (9.8%) had undergone colonoscopy. Compared with controls, case patients were less likely to have undergone any attempted colonoscopy OR, 0.69 [95% CI, 0.63 to 0.74;) or complete colonoscopy OR, 0.63 [CI, 0.57 to 0.69;). Complete colonoscopy was strongly associated with fewer deaths from left-sided CRC OR, 0.33 [CI, 0.28 to 0.39]) but not from right-sided CRC (OR, 0.99 [CI, 0.86 to 1.14]). For death from left-sided cancer, the association with colonoscopy 6 to 24 months before diagnosis was similar (OR, 0.46 [CI, 0.36 to 0.57]) to the association with colonoscopy more than 24 months before diagnosis (OR, 0.38 [CI, 0.32 to 0.45]). In contrast, for death from right-sided cancer, the association with colonoscopy 6 to 24 months before diagnosis was stronger (OR, 1.32 [CI, 1.10 to 1.59]) than the association with colonoscopymore than 24 months before diagnosis (OR, 0.92 [CI, 0.79 to 1.08]).	**IV** In usual practice, colonoscopy is associated with fewer deaths from CRC. This association is primarily limited to deaths from cancer developing in the left side of the colon. The strong inverse association between colonoscopy and death from left-sided but not right-sided CRC may be due in part to inadequate colonoscopy Although plausible as a partial explanation, inadequate colonoscopy is unlikely to fully explain this finding because the associations of colonoscopy and death from right- and left-sided CRC were the same for complete colonoscopy and any attempted colonoscopy For right-sided CRC, colonoscopy done more than 24 months before diagnosis was not associated with CRC death, whereas colonoscopy done within 6 to 24 months of diagnosis was associated with an increased risk for right-sided CRC death (OR, 1.32 [CI, 1.10 to 1.59]). The mechanism of this finding is clearly speculative, but false-negative colonoscopy may be 1 factor, because colonoscopy is more likely to miss right sided cancer and delay in diagnosis after a false-negative result might lead to worse outcomes.

Quality assessment: result: adequate definition of cases by record linkage; consecutive representative series of cases; community based controls matched with respect to age, sex, , income quintile (based on the mean household income of the enumeration area of residence), residence, selected from population registers.; ascertainment of exposure by record linkage; same method of ascertainment for cases and controls; non respondent described. . Adjustment for confounding by multivariate logistic regression. Covariates were age comorbid condition, sex, age (_70 or _70 years at diagnosis), and site of cancer (right-sided, left-sided, or unknown site

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Brenner 2007a	to estimate the proportions of colorectal cancer cases that might be prevented by sigmoidoscopy compared with colonoscopy among women and men population based Case control study USA	540 cases with a first diagnosis of primary colorectal cancer and 614 controls matched for age, sex, and county of residence detailed lifetime history of endoscopic examinations of the large bowel was obtained by standardized personal interviews, validated by medical records, and compared between cases and controls paying particular attention to location of colorectal cancer and sex differences	Proportion of preventable cancers by sigmoidoscopy	Estimated proportion of total colorectal cancer cases preventable by sigmoidoscopy: assuming that sigmoidoscopy reaches the junction of the descending and sigmoid colon only and findings of distal polyps are not followed by colonoscopy: 45% among both women and men,. Estimated proportions of total colorectal cancer preventable by sigmoidoscopy assuming that sigmoidoscopy reaches the splenic flexure and colonoscopy is done after detection of distal polyps: 50% and 55% (73% and 91% of total colorectal cancer preventable by primary colonoscopy) among women and men, respectively.	**IV** colonoscopy provides strong protection against colorectal cancer among both women and men. The proportion of this protection achieved by sigmoidoscopy with follow-up colonoscopy in case of distal polyps may be larger than anticipated. Among men, this regimen may be almost as effective as colonoscopy, at least at previousperformance levels of colonoscopy.

Quality assessment: result: adequate definition of cases by record linkage; consecutive representative series of cases; community based controls matched with respect to age, sex, and county of residence, randomly selected from population registers.; ascertainment of exposure by structured interview; same method of ascertainment for cases and controls; non responded described.

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Brenner 2007b	to estimate whether and to what extent these gender in the CRC incidence differences might be relevant for defining age at initiation of CRC screening among women and men retrospective cohort study USA	113 174 men and 113 454 women who died of CRC in the US in 2000–2003. Age and sex specific data on CRC incidence and mortality were obtained for the years 2000–2003 in the US from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Programme. The World Health Organisation (WHO) mortality Database 2006) was used to assess the consistency of observed patterns between populations.	cumulative 10-year incidence and mortality of CRC among men and women	Among men, cumulative incidence in the subsequent 10 years increased from 0.8% at age 50 to 1.2% at age 55 and 1.9% at age 60 Among women, comparable levels of 10-year cumulative incidence were reached at ages 54, 60, and 66 only, i.e. 4, 5, and 6 years later, respectively. Sensitivity analyses using 5- and 15- rather than 10-year cumulative incidence and mortality in the US as indicators of CRC risk yielded very similar differences in the age at which comparable levels were reached among men and women	**III** gender specific differentiation of age at initiation of CRC screening by about 5 years might help to utilise screening resources in a more efficient manner. Gender specific screening schedules should therefore deserve careful attention in the design and evaluation of CRC screening programmes.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Non exposed cohort drawn from the same community; Ascertainment of exposure: secure record; Assessment of outcomes by record linkage

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Brenner 2008	to assess differences in CRC incidence and mortality within Europe, in view of the potential implications regarding variation of age at screening initiation between countries. retrospective color study USA	113 174 men and 113 454 women who died of CRC in the US in 2000–2003. Estimates of CRC incidence and mortality rates for age groups 15–44, 45–54, 55–64, and 65þ years were obtained for 38 European countries from the GLOBOCAN 2002 database.	Incidence and cancer mortality among men and women in 38 European Countries	CRC incidence strongly increased with age in all countries. Estimates of median incidence (mi) across countries among men aged 50, 55 and 60 years were 37, 73, and 112 per 100 000 persons per year, respectively. The age at which these levels were reached among men and women in the different countries, denoted agemi50, agemi55, and agemi60, respectively, varied strongly.	**III** gender specific our analyses do not allow deriving a general recommendation regarding the best age for initiation of CRC screening in each country. Our results do suggest, however, that the optimal age for screening initiation is likely not to be the same for European countries and that variation by up to 10 years or even more across countries might be warranted because of major differences in CRC incidence and mortality

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Non exposed cohort drawn from the same community; Ascertainment of exposure: secure record; Assessment of outcomes by record linkage

Author, publication year	Comparator test	Study Objective Study design	Study Participants	Outcomes	Results	Conclusion Level of evidence
Butterworth A., 2006	First degree relative of patient with CRC	to obtain estimates of age-specific relative risk for different family history categories, and to convert these relative risk estimates into absolute risks, taking into account competing causes of mortality. Systematic review and meta-analysis of cohort, case-control and cross-sectional studies	60 studies of which: 43 case-control o cross-sectional studies; 17 prospective or retrospective cohort study design. Risk estimates for meta-analysis from 59 studies (2 studies reported on the same study); all studies estimated the relative risk associated with a family history of colorectal cancer. 47 studies estimated the relative risk of developing colorectal cancer given at least one affected first-degree relative	Relative and absolute risk of CRC	**One first-degree relative affected** RR: 2.24 (95% CI 2.06-2.43) **Any relative affected** RR: (13 studies): 1.75 (95% CI 1.44-2.12) **At least 2 affected first-degree relatives** RR: (13 studies): 3.97 (95% CI 2.60-6.06) **Cumulative absolute risks of colorectal cancer** over the next 10 years : <1% regardless of family history, until the age of 40, after 40 years: 2.5%: general population 4.7% (95% CI 4.0 to 5.6): at least one affected first-degree relative 9.6% (95% CI 6.3 to 14.2) for two or more affected first degree relatives **Cumulative absolute risks for mortality from CRC** Until the age of 45, 0.75% (~1 in 130) for the general population, 1.4% (~1 in 70) for individuals with at least one affected first-degree relative and 4.1% (1 in 24) for those with two or more first-degree relatives with colorectal cancer.	**III** This study adds to the evidence that having a first-degree relative affected with colorectal cancer approximately doubles the individual's risk of developing the same cancer compared to someone with no family history. The study also shown that having multiple affected relatives or being younger both increase that risk further. These relative risk estimates are translated into increases in absolute risk, although the magnitude of the increases vary depending up on the time-period specified. Using this information appropriate counselling, surveillance, or treatment can be administered based upon the most reliable and accurate available evidence.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Engelstad L.P,, 2001	To evaluate the effectiveness of a comprehensive and aggressive follow-up program aimed at increasing the proportion of low-income women who receive follow-up for Pap smear abnormalities found in the Emergency departement setting. RCT USA	108 women with abnormal Pap smear results after screening in a public hospital emergency department No significant difference between groups with regard to age, ethnicity and language. Significant difference between groups with regard to insurance status and initial Pap smear result.	Abnormal pap smear Follow up strategies: Control group: women received a follow up appointment by telephone and a letter to confirm (n=54) Intervention group: women, in addition to telephone appointment an letter, were followed by a nurse case manager who gave each woman a reminder call before each appointment and called immediately after any missed appointment to reschedule and to stress the importance of following up; computerized tracking; universal colposcopy (n=54) If a woman in the control group had not kept any follow-up appointments in the 6-month interval, she was crossed over to the intervention Protocol.	Proportion of women who received the initial follow up and proportion of women who have a diagnostic resolution in 18 months	**Proportion of follow up, n (%)** Follow up in 6 months Intervention= 35 (65) Control group =22 (41) *p=0.012* Follow up in 6 months and resolution in 18 months Intervention= 27 (50) Control group =10 (19) *p=0.001* **Multiple logistic regression analysis of predictor of follow up** Follow up in 6 months Intervention= OR 3.98 (1.36-9.74) Control group= referent Age= OR 1.08(1.02-1.13) No insurance= OR 2.78(1.00-7.71) Has or unknown insurance=reference Asian or other race= OR 0.16(0.03-0.85) Caucasian, African-American and Hispanic=referent Follow up in 6 months and resolution in 18 months Intervention= OR 6.53 (2.39-17.84) Control group= referent Age= OR 1.06(1.00-1.12) Asian or other race= OR 0.06(0.01-0.61 Caucasian, African-American and Hispanic=referent	**II** In conclusion, low-income women are at high risk of being lost to follow-up after having an abnormal Pap smear result. This study demonstrates that case management, computerized tracking, and universal colposcopy significantly improves the rate of follow-up and diagnostic resolution of abnormal Pap smears when compared with traditional care among low income women screened in a non primary care setting. Moreover, these findings suggest that an aggressive follow-up strategy could well be expected to reduce morbidity and mortality attributable to cervical cancer in this high-risk population. Insurers of low-income women, notably Medicaid, could promote improved follow-up by reimbursing programs for evidence based, case-management expenses.

Author, publication year	Study Objective Study Design	Intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
Jepson R, 2000	to examine factors associated with the uptake of screening programmes and to assess the effectiveness of methods used to increase uptake.	Screening uptake for different factors; screening uptake comparing different interventions	<u>Determinant studies</u> (on factors associated with uptake of screening test for different disease) 65 studies included: 29 RCTs, 7 controlled trials, 4 quasi-RCTs, 22 cohort studies and one case–control study <u>Intervention studies</u> (on intervention to increase uptake of screening programmes) 190 studies included 130 (68%) RCTs, 33 controlled trials, 27 quasi-RCTs 65% of intervention studies were undertaken in the USA or Canada	Determinant of screening uptake: age, insurance, status, previous screening behaviour. Intervention to increase screening uptake: educational intervention, counselling, invitation appointments, ecc	**Determinants of screening uptake** <u>Mammography</u> Women were more likely to attend if they had attended for a previous mammogram, had the intention to attend, had health insurance or received a recommendation to attend by their general practitioner <u>Papanicolaou (Pap) smear</u> women were more likely to attend if they had health insurance. Age was also a determinant (it was unclear whether older or younger women were more likely to attend) <u>FOBT screening</u> Being older than 65 years, previous participation in screening and being able to carry out the activities of daily living. <u>Prostate cancer screening</u> having a higher level of education and being African-American, as opposed to Caucasian. Determinants across the five main screening tests (also HIV antibody test) included attendance for a previous screening test and age. **Interventions to increase uptake of screening** <u>Limited effectiveness</u> printed and audio-visual educational materials; educational sessions; risk-factor questionnaires; and face-to-face counselling. <u>In-effective</u> the use of rewards or incentives <u>Effective</u> invitation appointments, letters (less effective for mammography) and telephone calls; telephone counselling; and removal of financial barriers (e.g. transport and postage costs)	I Individuals who previously participated in screening were more likely to be screened subsequently. Efforts could be focused on identifying and encouraging attendance among those who have never previously participated in screening. Current practice in the UK national screening programmes using invitation letters and/or appointments is supported by good evidence. Invitation telephone calls could also be considered, although the cost-effectiveness of this approach remains uncertain in the UK. All of these approaches could be considered for other screening tests. Reducing economic barriers (e.g. offering free postage or transportation costs) can increase uptake and may be appropriate for specific groups. Telephone counselling where barriers to screening are discussed could be considered. Healthcare professionals can be prompted either to perform or to recommend screening tests by using reminder systems such as tagged notes. Such reminder systems could be considered in secondary as well as primary care

					Intervention that may be effective educational home visits; opportunistic screening; multicomponent community interventions; simpler procedures; combination of different components aimed at individuals; reminders for non-attenders (for mammography only); and invitation follow-up prompts. Reminder interventions for physicians. combination of physician reminders and patient invitations:	

Quality of reporting (QUOROM CHECKLIST)

Methods search	databases , register, hand searching;	MEDLINE, BIDS Science Citation Index, Econlit, EMBASE, CANCERLIT, DHSS data, Dissertation Abstracts, ERIC, HealthSTAR, ASSIA , Pascal, SIGLE, Sociofile, PsycINFO, SHARE (Kings Fund), Library of Congress database, NHS CRD DARE, Cochrane Library
	Date restriction	From 1966 to 1998
	any restriction	No language restriction
Selection	Inclusion and exclusion criteria	Determinant studies (on factors associated with uptake of screening test for different disease Intervention studies (on intervention to increase uptake of screening programmes)
Validity assessment	Criteria and process used	Validity assessed with validated checklist
Data abstraction	Process used	Data abstracted by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed.
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	not reported
	summary results	Results presented narratively

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion
Ness R.M, 2000	To investigate the age-dependent cost-utility of one-time colonoscopic screening. Cost-utility analysiss USA	U.S. average-risk 40 year old population	One-time colonoscopic screening for colorectal cancer	QALY (quality-adjusted life year)	**Effectiveness of one-time screening** peaks around age 50 yr, whereas CRC related costs reach a minimum around age 60 yr for both men and women. Cohort of 100000: **QALYs /person** Male Never =18933 60-64=18978 55-59=18991 50-54=18999 45-49=19000 Female Never =20551 60-64=20600 55-59=20611 50-54=20616 45-49=20616 **Cost person ($)** Male Never =749 60-64=640 55-59=633 50-54=662 45-49=731 Female Never =676 60-64=574 55-59=581 50-54=625 45-49=690	One-time colonoscopic screening between 50 and 54 yr of age is cost-effective compared to no screening and screening at older ages in both men and women. Screening in men between 45 and 49 yr of age may be cost-effective compared to screening between 50 and 54 yr of age depending on societal willingness to pay

Marginal cost/QALY ($)
<u>Male</u>
Never =dominated
60-64= dominated
55-59=-
50-54=3625
45-49=69000
<u>Female</u>
Never = dominated
60-64=-
55-59=636
50-54=8800
45-49= dominated

Dominated means that the indicated strategy was of equal or less effectiveness than a less costly strategy

Sensitivity analysis
The marginal cost-utility of one-time colonoscopic screening is relatively insensitive to plausible changes in the cost of colonoscopy, the cost of CRC treatment, the sensitivity of colonoscopy for colorectal neoplasia, the utility values representing the morbidity associated with the CRC-related health states, and the discount rate.

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Newcomb 2003	To examine the association between sigmoidoscopy screening and colorectal cancer incidence. Population based Case control study	Case patients with distal (n = 1026) and proximal (n = 642) colorectal cancer 1294Community-based control subjects randomly selected according to the age and sex distribution of the case patients a structured 50-minute telephone interview to obtain information from the study subjects on known or suspected risk factors for colorectal cancer, including their screening histories prior to 1 year before diagnosis was undertaken	Associations between screening-only sigmoidoscopy and colorectal cancer incidence and between any sigmoidoscopy (including symptom-related) and colorectal cancer incidence.	Sigmoidoscopy was associated with a statistically significant and sustained reduction in the incidence of distal colorectal cancers. Compared with individuals who had never had a screening sigmoidoscopy, those who had ever had a screening had an OR for distal colorectal cancer of 0.24 (95% CI 0.17 to 0.33) The OR for distal colorectal cancer was also statistically significant when we included individuals with symptom-related sigmoidoscopies (i.e., "any test") in the analysis (OR _ 0.47, 95% CI_0.37 to 0.60).	**IV** Current recommendations regarding the frequency of sigmoidoscopy screening may be unnecessarily aggressive.

Quality assessment: result: adequate definition of cases by record linkage; consecutive representative series of cases; community based controls matched with respect to age, sex, , randomly selected from population registers.; ascertainment of exposure by structured interview; same method of ascertainment for cases and controls; non respondent described. . Adjustment for confounding by multivariate logistic regression. Covariates were age (in 5-year intervals), sex, family history of colorectal cancer, postmenopausal hormone use (females), level of education, smoking history, body mass index (BMI), and the number of previous tests (for individuals who had more than one sigmoidoscopy)

Author, publication year	Study design Study objective	Intervention	Participants	Outcome	Results	Level of evidence Conclusion
Sewitch 2007	To identify correlates of compliance with colorectal cancer (CRC) screening guidelines in average-risk population in Canada Cross-sectional survey	National survey addressing : **Independent study variables**: *Socio-demographic and lifestyle characteristics* : age, sex, education, country of birth, cultural/racial origin, daily servings of fruits and vegetables, number of alcoholic drinks in the past week, household income, employment, status and participation in physical activities in the past 3 months. *Clinical characteristics:* self-perceived general health, smoking status, chronic conditions, having a regular physician, bowel disease (Crohn's disease, ulcerative colitis), receipt of flu shots (over lifetime). *Psychosocial characteristics* : self-perceived mental health, life satisfaction, self-perceived stress and self-perceived work stress. *Environmental characteristics* : residential area, health region of residence, province, provincial per capita numbers of gastroenterologists and general practitioners in 2003, and provincial endoscopist fees **Dependent variable** : reported use of FOBT and endoscopy (sigmoidoscopy or colonoscopy	17,498 eligible (at least 50 years of age, without past or present CRC). respondents to a national survey	Association beteween sociodemographic , clinical , psychosocial , environmental characteristics and use of FOBT or endoscopy	70% were non-adherent CRC screening to guidelines. Specifically, 85% and 79% were non-adherent to FOBT and endoscopy, respectively. Correlates for all outcomes were**: having a regular physician :** FOBT: OR = 2.68; Endoscopy: OR 1.91; FOBT or endoscopy: OR 2.39 **getting a flu shot** FOBT: OR = 1.59; Endoscopy: OR 1.51; FOBT or endoscopy: OR 1.55 **having a chronic condition** FOBT :OR 1.32; Endoscopy: OR 1.48; FOBT or Endoscopy: OR 1.43. Greater physical activity, higher consumption of fruits and vegetables and smoking cessation were each associated with at least 1 outcome. Self-perceived stress was modestly associated with increased odds of compliance with endoscopy (OR: 1.07) and to FOBT or Endoscopy (OR = 1.06;	**V** Healthy lifestyle behaviors and factors that motivate people to seek health care were associated with compliance, implying that invitations for CRC screening should come from sources that are independent of physicians, such as the government, in order to reduce disparities in CRC screening.

Author, publication year	Intervention	Study design	Participants Country	Outcome	Results	Level of evidence Conclusion
Wee 2005 (1)	Mass screening for colorectal cancer by FOBT, sigmoidoscopy or colonoscopy	Cross-sectional survey	Random sample of US population aged 50-75 years n: 11.427 USA	Participation to screening by FOBT, sigmoidoscopy or colonoscopy. Factors affecting participation: age, ethnicity, educational level, body weight	Completed annual FOBT in the past year: 16% Completed sigmoidoscopy or colonoscopy in the past 5-10 years: 29% Completed FOBT or sigmoidoscopy or colonoscopy: 36% Reason for not having a FOBT: unaware that they needed: 64% physician not recommended: 22% Reason for not having a sigmoidoscopy or colonoscopy: unaware that they needed: 72% physician not recommended: 21% Factor associated with having any of the screening test: Body mass index <18.5: adjusted OR: 0.7 (CI95% 0.5-1.0) Older age: adjusted OR: 10.1 (CI95% 10.0-10.2) Ethnicity Hispanic adjusted OR: 0.7 (CI95% 0.6-0.8) Education <high school: adjusted OR 0.5 (CI95% 0.4-0.7) None insurance coverage: adjusted OR: 0.7 (CI95% 0.5-0.8)	**V** the prevalence of screening program is low. Main reason seem to be lack of awareness and inadequate provider counselling. Non White patients, those with lower educational level and poorer health care access were less likely to undergo a screening for colorectal cancer

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Zauber A.G., 2008	To assess life-years gained and colonoscopy requirements for colorectal cancer screening strategies and identify a set of recommendable screening strategies Decision analysis using 2 colorectal models (MISCAN and SimCRC) USA	U.S. average-risk 40 year old population	Faecal occult blood tests (FOBTs), flexible sigmoidoscoy, or colonoscopy screening beginning at age 40, 50, or 60 years and stopping at age 75 or 85 years, with screening intervals of 1, 2, or 3 years for FOBT and 5, 10, or 20 years for sigmoidoscopy and colonoscopy.	Number of life-years gained compared with no screening and number of screening tests required.	Beginning screening at age 50 years was consistently better than at age 60. Decreasing the stop age from 85 to 75 years decreased life-years gained by 1% to 4%, whereas colonoscopy use decreased by 4% to 15%. Assuming equally high compliance, 4 strategies provided similar life-years gained: colonoscopy every 10 years, annual Hemoccult SENSA (Beckman Coulter, Fullerton, California) testing or faecal immunochemical testing, and sensitive FOBT every 2 to 3 years with 5-yearly sigmoidoscopy. Hemoccult II and flexible sigmoidoscopy every 5 years alone were less effective. **Sensitivity analysis** The results were most sensitive to beginning screening at age 40 years.	The results support colorectal cancer screening with colonoscopy every 10 years, a sensitive FOBT annually, or high sensitive FOBT every 2 to 3 years with a 5-yearly flexible sigmoidoscopy from ages 50 to 75 years. Findings in general support the 2002 USPSTF recommendations for colorectal cancer screening, with a few exceptions. First, while there is currently no recommended stopping age for colorectal cancer screening, this study found that continuing screening after age 75 in individuals who have had regular, consistently negative screenings since age 50 provides minimal benefit for the resources required. Second, it was found that screening with Hemoccult II annually and flexible sigmoidoscopy alone every 5 years does not provide effectiveness similar to that of screening annually with a sensitive FOBT or every 10 years with colonoscopy. Finally, if a sensitive FOBT is used, the FOBT screening interval can be extended to 3 years when used in combination with flexible sigmoidoscopy every 5 years.

3
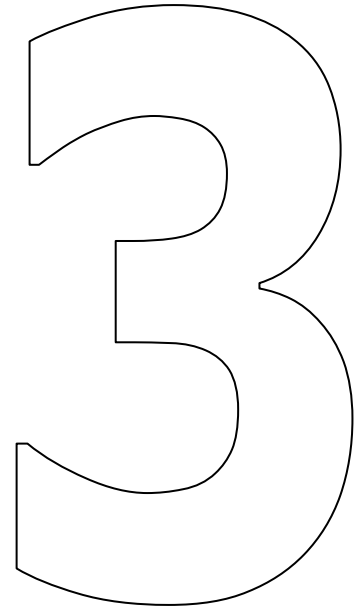
Evaluation and interpretation of screening outcomes
EVIDENCE

EU CRC Guidelines Literature Group

3.1 Flexible sigmoidiscopy and colonoscopy

3.1.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 1

Which early performance indicators were used for the monitoring of CRC screening programmes in trials or other screening programmes?

PICOS

P: General population aged 50 years and older
I: Offering crc screening (or other cancers if not available for CRC)
C: Not applicable
O: Early performance indicators
S: RCT's, systematic reviews of RCT's, reports on established programs

CLINICAL QUESTION 2

What are the coverage and participation rates achieved in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering CRC screening
C: Not applicable
O: Coverage and participation
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 3

What are the detection-rates of cancers/adenomas achieved in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy, or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Detection-rates of cancers/adenomas
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 4

What are the positive rates achieved in studies of CRC screening using FOBT(guaiac/immunology), flexible sigmoidoscopy?

PICOS

P: Ggeneral population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Positive rates
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 5

What is the uptake of colonoscopy achieved in studies of CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Uptake of colonoscopy
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 6

What proportion of screen detected cancers achieved in studies of CRC screening is stage I or II, based on TNM classification, for CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Proportion of stage I and II screen detected cancers (based on TNM classification)
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 7

What are the positive predictive values of the screening test using FOBT (guaiac/immunology), or flexible sigmoidoscopy for cancer/precancer lesions achieved in studies of CRC screening?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Positive predictive values, of the screening test
S: RCT's, systematic reviews of RCT's, observational studies, reports on established programs

CLINICAL QUESTION 8

What are the rates of adverse effects (deaths within 30 days/early bleeding/perforation) of screening colonoscopy or a colonoscopy following a positive test observed within a CRC screening programme using FOBT(guaiac/immunology), or flexible sigmoidoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Rates of adverse effects (deaths within 30 days / early bleeding / perforation) of colonoscopy following a positive test
S: RCT's, systematic reviews of RCT's, observational studies, reports of established programs

CLINICAL QUESTION 9

What are the rates of inadequate tests using FOBT (guaiac/immunology), flexible sigmoidoscopy or colonoscopy achieved in studies of CRC screening?

PICOS:

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Rate of inadequate tests
S: RCT's, systematic reviews of RCT's, observational studies, reports of established programs

CLINICAL QUESTION 10

What are the rates of incomplete screening colonoscopies and sigmoidoscopies and follow-up colonoscopies?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Rates of incomplete screening colonoscopies and sigmoidoscopies and follow-up colonoscopies **S**: RCT's , systematic reviews of RCT's, observational studies, reports of established programs

CLINICAL QUESTION 11

What is the proportion of benign lesions referred for surgery?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Proportion of benign lesions referred for surgery
S: RCT's, systematic reviews of RCT's, observational studies, reports of established programs

CLINICAL QUESTION 12

What is the proportion of malignant adenomas endoscopically treated?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Proportion of malignant adenomas endoscopically treated
S: RCT's, systematic reviews of RCT's, observational studies, reports of established programs

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic.

RESULTS

We found 10 studies relevant for the questions of this chapter. Four assessed the outcomes for sigmoidoscopy (1, 2, 4, 5) three for colonoscopy (6,7,9) one compared the outcomes between FOBT and sigmoidoscopy (8) and one compared the outcomes between FOBT, colonoscopy and sigmoidoscopy (3)

Early performance indicators used in the retrieved studies were:

For FOBT trials:
Participation rate
Positive rate
Rate of further investigation for positives(colonoscopy)
Detection rate of cancer and adenomas

For FS and CT trials:
Participation rate
Positive rate
Rate of further investigation for positives(colonoscopy)
Detection rate of cancer and adenomas
Inadequate test
Incomplete test
Complication
Stages of detected cancer

The studies on colonoscopy were all cross-sectional surveys assessing the positive rates, detection rates of advanced neoplasia and complications in large samples of subjects (50,148, 1,539, 3,196) at average risk of colorectal cancer aged 40-79 years. One was conducted only with men (7), one only with women (6) and the third (9) with participant of both sexes. Characteristics of studies and results are presented in detail in the attached table and summarized in the table below.

Results of studies on colonoscopy

	Schoenfeld 2005	Lieberman 2000	Regula 2006
Participants	1539 women aged 50-79 at average risk	3,196 men aged 50-75. High percentage of participants with family history of CRC	50,148 male and female aged 50-66 at average risk
Q 4: positive rates	20.4%	53.8%	25%
Q 3: cancer or	any adenomas or cancer:	any adenoma or cancer:	any adenoma or cancer:

adenomas detection rates	20.4%; advanced neoplasia: 4.9%	37.5%; advanced neoplasia: 10.5%	14.9%; advanced neoplasia 6.8%
Q 8 complication	0%	0.3%	0.1%
Q9-Q10Incomplete examination	1.3%		8.9%
Q 6:stage I,II	Not reported	73.3%	62.5%

All studies report data on prospective cohorts of consecutive asymptomatic patients attending endoscopy clinics, in one case (Regula) following general practitioners' advice to undergo screening. No study was designed to assess participation rates

Basing on their data Schoenfeld and Lieberman calculated how many advanced lesions (cancer and advanced adenomas) had been missed if only a sigmoidoscopy would have been done. Lieberman calculated that if FS had been performed examining colon until the splenic flexure followed by colonoscopy if adenoma had been found, 79.9% of advanced neoplasia would have been identified.

If FS had been performed only until the junction of the descending colon to the sigmoid, 68.1% of advanced neoplasia would have identified.

Schoenfeld calculated that if only FS had been performed advanced colorectal neoplasia have been identified in 1.7% and missed in 3.2% of participants. 35.2% of advanced neoplasia would have been identified by FS alone. If distal colon had been defined as rectum and sigmoid 94% of advanced neoplasia would have been missed. If distal colon had been defines as rectum, sigmoid and descending colon and FS would have been performed to the splenic flexure, 92.3% of advanced neoplasia would have been missed.

The studies on sigmoidoscopy are all ongoing RCTs with the aim to assess the effect of sigmoidoscopy screening on CRC mortality and incidence. The published retrieved studies are cross-sectional surveys reporting the results of the baseline assessment (1,2,4,5).

Characteristics of studies and results are presented in detail in the attached table and summarized in the table below.

Results of studies on flexible sigmoidoscopy

	SCORE 2002	PLCO 2005	UK FS SCREENING TRIAL 2002	NORCCAP 2003
Participants	17148 participants at average risk aged 55-64	77465 participants at average risk aged 55-74 years	57254 participants at average risk aged 55-64 years	20003 participants at average risk aged 55-64 years
Q 2: compliance	58.3%	83.5%	71%	65%
Q 4: positive rates	17.6%	23.4%	27.7%	20.4%
Q 5 further investigation	8.3%	17.3%	5.3%	19.5%
Q 3: cancer or adenoma detection rates	Any adenoma or cancer: 11.3%; advanced neoplasia:3.4% detection rate for cancer: 5.4/1000	Any adenoma or cancer 9%; advanced neoplasia: 4.47% detection rate for cancer: 2.9/1000	Any adenoma or cancer:12.4%; advanced neoplasia: 5%; detection rate for cancer: 3.5/1000	any adenoma or cancer: 12%; advanced neoplasia: 2.8% detection rate for cancer: 3.2/1000
Q 8 complication of colonoscopy	1.2%	Not reported	0.5%	Not reported
Q9 inadequate test	12.7%	11%	Not reported	Not reported
Q 10 Incomplete examination	7.5%	Not reported	Not reported	Not reported
Q 6:stage I,II	Dukes A:54%	stage I : 58.6% stage II: 18.3% of people with cancer	Dukes A: 62% of cancers Dukes A or B: 74%	Not reported

Finally we retrieved two randomised controlled trials comparing FS vs FOBT(8) and FS vs colonscopy and FOBT (3)

Characteristics of studies and results are presented in detail in the attached table and summarized in the table below

Summary results of randomised controlled trials

	SCORE 2	SCORE 3
Participants	26682 participants at average risk aged 55-64 years	18477 participants at average risk aged 55-64 years
Q 2: compliance	FOBT (1+2): 28.6% FS (3+4): 28.1% Patient choice (5): 27.1% (14.6% FOBT, 12.5% FS)	FOBT: 32.3% FS: 32.3% Colonoscopy :26.5%
Q 4: positive rates	FOBT (1+2+5): 4.3% FS (3+4+5): 18.6%	FOBT: 4.7% FS: 18.9% Colonoscopy :31.1%
Q 5 further investigation	FOBT (1+2+5): 4.3%; FS (3+4+5):7.6%	FOBT: 4.7%; FS: 7.2%
Q 3: cancer or adenomas detection rates	FOBT (1+2): 1.8% cancer detection 3.4/1000 FS (3+4+5): 5.1% cancer detection rate:3.5/1000	FOBT: 1.2% FS: 11.8% Colonoscopy :18%
Q 8 complication of colonoscopy	0.3%	
Q9 inadequate test	FS(3+4+5): 8.1% (FS)	FS: 1.1% Colonoscopy: 2.1%
Q 10 Incomplete examination	FOBT (1+2+5):23.3% (colonoscopy) FS(3+4+5):12.9%(FS) FS(3+4+5):13% (colonoscopy)	Colonoscopy: 13,2%

CONCLUSIONS

Compliance. The results are very different and generally not comparable across studies. With the exception of the Norvegian study, the trials assessing effectiveness of FS screening enrolled people interested in screening; similarly colonoscopy studies were not designed to assess compliance as they were not conducted in the context of a screening programme (Liebermann, Schoenfeld) or the information on the number of people invited to undergo screening was not reported (Regula). Information on participation rates can be derived from the Norwegian trial and from the two trials comparing different screening strategies, as they enrolled a random sample of the general average risk population. In the Norwegian trial the attendance rate was 68% among people invited to have FS and 65% among people invited to have FS and FOBT. The participation rates were lower (28%-32%) in the Italian trials comparing FIT, FS and colonoscopy used alone or in combination: no significant difference was observed between FS and FIT, while participation rate to colonoscopy was significantly lower compared to the other two strategies.

Detection rate: the baseline results of the FS screening trial are fairly consistent with respect to the DR of CRC and advanced adenomas and to the stage distribution of CRC. When compared with FS or colonoscopy the DR of CRC and advanced adenomas with FIT on a single screening round is significantly lower. The DR of colonoscopy is higher that the DR of FS even if the only study comparing directly the two methods would suggest that the gain in neoplasia yield with colonoscopy may be present only among people older than 60. With the exception of the Schoenfeld study, all other studies, including the only trial comparing people randomly allocated to FS or colonoscopy, indicate that FS could detect about 70% of advanced neoplasms detected by colonoscopy. Also, while the Schoenfeld study suggested a different yield of advanced neoplasia for FS among men and women, this finding has not been reported in other studies. (LEVEL OF EVIDENCE II,V)

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3.1.2 Evidence tables (see 3.4.2)

3.2 FOBT screening

3.2.1 Summary document

Silvia Minozzi

METHODS

In the first instance information was extracted from the randomised controlled trials of colorectal cancer screening using FOBt.[1-4] Information was also extracted from the Cochrane review: screening for colorectal cancer using the faecal occult blood test, Hemoccult.[5]

CLINICAL QUESTION 1

What early performance indicators were used for the monitoring of CRC screening programmes in trials or other screening programmes (Italy, UK).

PICOS

P: General population aged 50 years and older
I: Offering crc screening (or other cancers if not available for crc)
C: Not applicable
O: Early performance indicators
S: RCTs, systematic reviews of RCTs, reports on established programmes

RESULTS

Very little information was given on early indicators in the RCT papers reviewed so far, however, there has been a recent review of the best surrogate endpoints for cancer screening trials (based on the UK FlexiSig trial)[6].

CONCLUSIONS

Further investigation is needed to determine whether there is evidence relating to early indicators in FOBT screening.

CLINICAL QUESTION 2

What are the coverage and participation rates achieved in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Coverage and participation
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

In the RCTs of FOBT screening using Hemoccult, participation rates ranged from 53.4% to 94%. The higher participation percentages (attended/invited) were only seen in second and subsequent screening rounds in the Funen study, as those who had not attended the first round of screening were not invited again. The participation rates of the first round of screening ranged from 54%-66.8%.

CONCLUSIONS

Participation rates were very dependent on the methodology used for each study and the invitation strategy used. Coverage and participation information from established screening programmes across the world should be available in the future (ICRCSN).

CLINICAL QUESTION 3

What are the detection rates of cancers/adenomas achieved in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy, or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Detection rates of cancers/adenomas
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

The CRC incidence rates were given for the Funen, Minnesota and Nottingham trials. They were: Funen, 2.06/1000py in screened (compared with 2.02/1000py in controls); Minnesota, 32-33/1000 in screened (compared with 39/1000 in controls) and Nottingham, 1.51/1000py in screened (compared with 1.53/1000py in controls).

CLINICAL QUESTION 4

What are the positive rates achieved in studies of CRC screening using FOBT(guaiac/immunology), flexible sigmoidoscopy or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Positive rates
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

In the RCTs of FOBT screening using Hemoccult, the positivity rates varied depending on whether the slides were rehydrated or not. For rehydrated slides the positivity rate ranged from 1.7%-15.4%. For unrehydrated slides the positivity rate ranged from 0.8%-5.3%.

CONCLUSIONS

Positivity rates were dependent on the method of slide handling used with a wider range of rates seen for rehydrated slides. Information on positivity rates from established screening programmes across the world should be available in the future (ICRCSN).

CLINICAL QUESTION 5

What is the uptake of colonoscopy achieved in studies of CRC screening using FOBT(guaiac/ immunology), flexible sigmoidoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Uptake of colonoscopy
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

The Nottingham RCT was the only one of the RCTs to report on colonoscopy uptake. In this study there was a 73% uptake of colonoscopy (with other participants also undergoing alternative assessments such as barium enema).

CONCLUSIONS

Other data sources need to be investigated in order to provide additional evidence in relation to this question.

CLINICAL QUESTION 6

What proportion of screen detected cancers achieved in studies of CRC screening is stage I or II, based on TNM classification, for CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Proportion of stage I and stage II screen detected cancers (based on TNM classification).
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

In the Cochrane review, stage at diagnosis was reported using Dukes' classification for all 4 RCTs (no study reported using TNM classification). The proportion of cancers which were stage A ranged from 22%-30% and the proportion stage B ranged from 26%-34%.

CONCLUSIONS

Other data sources need to be investigated in order to provide additional evidence in relation to this question. Information on stage at diagnosis from established screening programmes across the world should be available in the future (ICRCSN).

CLINICAL QUESTION 7

What are the positive predictive values of the screening test using FOBT (guaiac/immunology), or flexible sigmoidoscopy for cancer/precancer lesions achieved in studies of CRC screening?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Positive predictive values of the screening test
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

In the Cochrane review, positive predictive value for both CRC and adenoma were given for three of the trials (Nottingham, Funen and Minnesota). The PPV for CRC ranged from 5.2%-18.7% when the slides were not rehydrated (0.9%-6.1% in the Minnesota trial when the slides were rehydrated). The PPV for adenoma ranged from 14.6%-54.5% when the slides were not rehydrated (6%-11% in the Minnesota trial when the slides were rehydrated).

CLINICAL QUESTION 9

What are the rates of inadequate tests in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy or colonoscopy?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Rate of inadequate tests
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS:

No data were provided on this topic in the RCTs.

CONCLUSIONS

Other data sources need to be investigated in order to answer this question.

CLINICAL QUESTION 10

What are the rates of incomplete screening colonoscopies and sigmoidoscopies and follow-up colonoscopies?

PICOS

P: General population aged 50 years and older
I: Offering crc screening
C: Not applicable
O: Rates of incomplete screening colonoscopies and sigmoidoscopies and follow-up colonoscopies
S: RCTs, systematic reviews of RCTs, observational studies, reports on established programmes

RESULTS

The Funen RCT was the only one of the RCTs to report on incomplete colonoscopies. In this study a complete examination of the colon was performed in 89% of subjects with positive FOBT during the 9 rounds, but 2.6%-7% had no colonic examination.

CONCLUSIONS

Other data sources need to be investigated in order to provide additional evidence in relation to this question.

CLINICAL QUESTIONS 8, 11 AND 12

No information was available from the RCTs of FOBT for colorectal cancer screening or the Cochrane review of colorectal cancer screening using Hemoccult in relation to these questions.

Question Number	Funen	Goteborg	Minnesota	Nottingham	UK Pilot (1st round)
1. Early performance indicators	Colorectal cancer and adenoma detection?				
2. Coverage and participation rates See Cochrane table 4 below for results from the Cochrane review	Compliance in the 9 rounds of screening: (Only respondents at each round were invited to subsequent rounds) Round 1: 67% Round 2: 93% Round 3: 94% Round 4: 94% Round 5: 92% Round 6: 92% Round 7: 93% Round 8: 92% Round 9: 91%		Mean of 75% participation in annual group and 78% in the biennial group.		478,250 invited 56.8% uptake (i.e. testing completed)
4. Positivity rates See Cochrane table 6 below for results from the Cochrane review	Proportion of subjects H-II positive (not rehydrated): Round 1: 1.0% Round 2: 0.8% Round 3: 0.9% Round 4: 1.2% Round 5: 1.8% Round 6: 3.8% Round 7: 1.7% Round 8: 1.1% Round 9: 1.4%		See Appendix (Minnesota Table 2)	2.6% cumulatively over all the screening rounds (participants were offered FOB tests between three and six times)	1.9%
9. Inadequate test rates	No Data	Unavailable to the authors when preparing this table			No Data
10. incomplete colonoscopies/sigmoidoscopies	A complete examination of the colon was performed in 89% of subjects with positive H-II during the 9 rounds, but 2.6%–7.0% had no colonic examination. Complete information is given in appendix (Funen Table IV)				3700 of 4116 completed 89.9% completion rate

Question Number	Funen	Goteborg	Minnesota	Nottingham	UK Pilot (1st round)
5. colonoscopy uptake		Colonoscopy was not the first-line diagnostic investigation	83% (annual) – 84% (biennial) underwent diagnostic follow-up, including a complete examination of the barge bowel by colonoscopy or the combination of double-contrast barium enema and sigmoidoscopy	73% (others had alternatives such as barium enema)	4116 colonoscopies (of 5050 with positive tests) – 81.5%

76(1.5%) medically unfit
858(16.9%) did not attend
69(8%) recently undergone colonoscopy in private clinic
17(2%) had no colon |
| 3. detection rates (cancers and adenomas)
See Cochrane table 5 below for results from the Cochrane review | Colorectal cancer incidence rate: 2.06 per 1,000 person years | | | Colorectal cancer incidence rate: 1.51 per 1,000 person years | Cancer detection = 1.62 per 1000 screened

Neoplasia detection = 6.91 per 1000 |
| 6. proportion of screen detected cancers are TNM stage I or ll
See Cochrane table 7 below for results from the Cochrane review | 36% Dukes A in H-II positive cases | | | | Described using Dukes stage:

22% polyp cancers
26% stage A
25% stage B |
| 7. ppv of screening test

See Cochrane table 6 below for results from the Cochrane review | Predictive value for each screening round is given in appendix (Funen Table V) | | Annual: 0.87% for one positive slide to 4.53% for six positive slides. Biennial: 1.12%-6.13%. Table 2 | | 10.9% for invasive cancer

35% for adenoma |
| 20-21. false positive rate. False negative rate | CRC: 81.3%-94.8%
Adenoma: 61.7%-85.4% | | CRC: 93.9%-99.1%
Adenoma: 89%-94% | CRC: 82.9%-90.1%
Adenoma: 45.5%-57.2% | CRC:89.1%
Adenoma: 65% |
| 11. proportion of benign lesions referred for surgery | No Data | | | | No data |

Question Number	Funen	Goteborg	Minnesota	Nottingham	UK Pilot (1st round)
12. proportion of malignant adenomas endoscopically treated	No Data				No data
8. complication of colonoscopy	No Data				10 patients (0.24%) admitted overnight for observation because of bleeding or abdominal pain. 13 (0.32%) readmitted for same reasons 2 (0.05%) had perforations

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3.2.2   Evidence tables (see 3.4.2)

3.3   Update data from screening programs implemented in the community (FOBT, flexible sigmoidoscopy)

3.3.1   Summary document

Silvia Minozzi

METHODS

Bibliographic search performed in MedLine form 2000 to December 2008 with the following search strategy:

(exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (faecal occult blood test* OR faecal occult blood test* or occult blood (Mesh) OR guaiac OR guaiac (Meesh) OR immunochemical OR sigmoidoscopy OR colonoscopy OR colonoscopy (mesh)

RESULTS

13 articles have been retrieved, 11 reporting the results of FOBT screening and 2 on sigmoidoscopy . Two are RCTs (5, 13) , the other are cross-sectional surveys reporting the results of screening programs implemented in the community.

Early performance indicators used in retrieved studies were:

For FOBT trials:
Participation rate
Positive rate
Rate of further investigation for positives(colonoscopy)
% of incomplete colonoscopy
Detection rate for cancer
Detection rate for high-risk adenoma
Detection rate for low-risk adenoma
Detection rate for any neoplasia
Stage of detected cancer
Positive predictive value for cancer
Positive predictive value for high-risk adenoma
Positive predictive value for advanced adenoma
Positive predictive value any neoplasia

For FS and CT trials:
Participation rate
Positive rate
Rate of further investigation for positives(colonoscopy)
Detection rate of cancer and adenomas
Inadequate test
Incomplete test
Complication
Stages of detected cancer

FOBT

Study	Study characteristics	Q2 coverage - participation	Q3 detection rate for cancer /adenoma	Q4 positivity rate	Q5 uptake of colonosocpy	Q6 % of stage I,II cancer	Q7 PPV for cancer/ precancer	Q8 % of adverse events	Q9 % of inadequate test	Q10 % of incomplete colonoscopy and FS	Q11 % of benign lesion	Q12 % of malignant adenoma
Chrissidis 2004	4189 subjects over 50 years, Hemoccult, 3 tests, Grece	49%	Polypoid lesion: 9.7%	8.5%	89%			0		28%		0
Crotta 2004	2961 subjects aged 50–74 years, 1 day I-FOBT ,Italy	55.1%	Cancer: 1.8 ‰ Adenoma: 16.6 ‰	4.4%	93.1%	1 T1 1 T2 1 T3	Cancer: 4.5% Adenoma: 40.3%			6%		
Denis 2007	182 981 residents aged 50–74 years. GUAIAC , France	55.4%	Cancer: 2.3 ‰ Neoplasia: 12.8‰	3.4%	87.9%	St I: 47.6% St II: 23.8%	Cancer: 7.6% Adv Adenoma: 23.6%	0.2%		5%		
Federici 2006	1449 subjects aged 50-74 years. RCT Italy	17.2%										

FOBT cont

Study	Study characteristics	Q2 coverage - participation	Q3 detection rate for cancer /adenoma	Q4 positivity rate	Q5 uptake of colonosocpy	Q6 % of stage I,II cancer	Q7 PPV for cancer/ precancer	Q8 % of adverse events	Q9 % of inadequate test	Q10 % of incomplete colonoscopy and FS	Q11 % of benign lesion	Q12 % of malignant adenoma
Hart 2003	1828 employees aged 41–65 years, Hemoccult, UK	25.4%		1%								
Peris 2007	63880 subjects aged 50-69 years, Guaiac, Spain	17.2% 1° round 22.3% 2° round	1° round Cancer: 2.1 ‰ High risk ad: 7.2 ‰ Any neoplasia: 11.3 ‰ 2° round Cancer: 0.9 ‰ High risk ad: 2.8 ‰ Any neoplasia: 4.2 ‰	3.4% 1° round 0.8 % 2° round	1° round: 89.8% 2° round: 87.8%	Stage I: 41.7% Stage II: 19.4% Stage III: 27.8%	1° round Cancer: 6.2% High risk ad: 21.2% Adv adenoma: 33.3% 2° round Cancer: 10.6 % High risk ad: 34.1% Adv adenoma: 50.4%	0.96%	1° round: 3.6% 2° round: 4.5%	7.7%		

FOBT cont

Study	Study characteristics	Q2 coverage - participation	Q3 detection rate for cancer /adenoma	Q4 positivity rate	Q5 uptake of colonosocpy	Q6 % of stage I,II cancer	Q7 PPV for cancer/ precancer	Q8 % of adverse events	Q9 % of inadequate test	Q10 % of incomplete colonoscopy and FS	Q11 % of benign lesion	Q12 % of malignant adenoma
Saito 2006	Subjects 40 years and older I-FOBT , Japan	17%		7.1%	60%							
Weller 2007	2° round of the UK CCSP. 127 746 subjects 50-69 years	1° round : 58.5% 2° round 52.1%	1° round : Any neoplasia 6.17 ‰ cancer: 1.35‰ 2° round Any neoplasia 5.67 ‰ Cancer: 0.94 ‰	1° round : 1.59% 2° round 1.77%	91.7%		1° round Cancer: 8.51% Any neoplasia: 38.8% 2° round Cancer 5.29% Any neoplasia: 32.1%		0.4%			

FOBT cont

Study	Study characteristics	Q2 coverage - participation	Q3 detection rate for cancer /adenoma	Q4 positivity rate	Q5 uptake of colonoscopy	Q6 % of stage I,II cancer	Q7 PPV for cancer/ precancer	Q8 % of adverse events	Q9 % of inadequate test	Q10 % of incomplete colonoscopy and FS	Q11 % of benign lesion	Q12 % of malignant adenoma
Grazzini 2004	1-day I-FOBT without any dietary restriction. 192 583 subjects aged 50–70	41%	Cancer: 2.5 ‰ High risk ad: 8.8 ‰ Low risk ad: 4.9 ‰	5.8%	75.3%		Cancer: 5.7% High risk ad: 20.3% Low risk ad: 11.2%					
Fenocchi 2006	I-FOBT without any dietary restriction 11734 subjects 50 years and older	90.1%	Cancer: 0.95% High risk ad: 1.24% Low risk ad: 0.93%	11.1%	86.8%	Early cancer: 14%	Cancer: 8.6% High risk ad: 11.2% Any neoplasia: 28.2%					
Malila 2008	GUAIAC; 52998 age 60-69 years. RCT	70.8%	Cancer: 8%	1.5%								

FS

Study	Study characteristics	Q2 coverage - participation	Q3 detection rate for cancer /adenoma	Q4 positivity rate	Q5 uptake of colonoscopy	Q6 % of stage I,II cancer	Q7 PPV for cancer/ precancer	Q8 % of adverse events	Q9 % of inadequate test	Q10 % of incomplete colonoscopy and FS	Q11 % of benign lesion	Q12 % of malignant adenoma
Brotherstone 2007	510 subjects 60-64 years, UK	55%										
Federici 2006	1538 subjects aged 50-74 years. RCT Italy	7%										
Vijala 2007	Subjects 55-64 years, Australia	1° round 23% 5 year recall: 42%	Adenoma: 14% Adv ad: 5% Cancer: 0.4% 5 year recall Adenoma: 11% Adv ad: 2.1% Cancer: 0			Stage I: 69% Stage III: 23% Stage IV: 7.5%						

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3.3.2 Evidence tables (see 3.4.2)

3.4 Adverse events of FOBT, sigmoidoscopy, colonoscopy

3.4.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 19

What is the rate of negative side effects of guaiac FOBT screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Guiac FOBT;
C: Not applicable
O: False-positive tests, false-negative tests, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCT's, pilot studies

CLINICAL QUESTION 20

What is the rate of negative side effects of immunological FOBT screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Immunological / immunochemical FOBT;
C: Not applicable
O: False-positive tests, false-negative tests, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCT's, pilot studies

CLINICAL QUESTION 21

What is the rate of negative side effects of flexible sigmoidoscopy screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Flexible sigmoidoscopy;
C: Not applicable
O: False-positive tests, false-negative tests, rates of perforations, bleeding and other serious adverse effects, complication rate at follow-up colonoscopy?
S: (Systematic reviews of) RCT's, pilot studies

CLINICAL QUESTION 22

What is the rate of negative side effects of colonoscopy screening?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older
I: Colonoscopy;
C: Not applicable
O: False-positive tests, false-negative tests, rates of perforations, bleeding and other serious adverse effects
S: (Systematic reviews of) RCT's, pilot studies

SEARCH METHOD

We contacted experts in the field to retrieve published articles on this topic

RESULTS:

We found 10 studies relevant for these questions. Four assessed the outcomes for sigmoidoscopy (1, 2,4,5) three for colonoscopy (6,7,9) one compared the outcomes between FOBT and sigmoidoscopy (8) and one compared the outcomes between FOBT, colonoscopy and sigmoidoscopy (3).One is a pilot study of screening by FOBT on the general population in the UK (10). For false positive and positive rate of FOBT we also considered the four published randomised controlled trials included in the Cochrane Systematic Review.

Complications of colonoscopy

	Lieberman 2000	Regula 2006	Schoenfeld 2005	Segnan 2005 (SCORE 2)	Segnan 2007 (SCORE 3)	UK CRC screening pilot 2004	UK FS screening trial Investigators 2002
Severe complications	0.3%	0.1%	0%	0.3%:	Not reported	0.05%	0.5%
Minor complications	Not reported	Not reported	Not reported	3.9%	Not reported	0.56%	0.4%

Complications of sigmoidoscopy

	Segnan 2007 (SCORE)	Segnan 2005 (SCORE 2)	Segnan 2007 (SCORE 3)	Weissfeld 2005 PLCO	UK FS screening trial Investigators 2002	NORCCAP study 2003
Severe complications	0.02%	0.02%	Not reported	Not reported	0.03%	Not reported
Minor complications	0.6%	0.5%	Not reported	Not reported	0.2%	Not reported

Adverse events of FOBT (Guaiac and immunochemical)

	Segnan 2005 (SCORE 2)	Segnan 2007 (SCORE 3)	UK CRC screening pilot	Nottingham trial	Funen trial	Goteborg trial	Minnesota trial	NORCCAP study 2003
FP rate	CRC or advanced adenoma: 54%	CRC or advanced adenoma: 71.6%	CRC:89.1% Adenoma: 65%	CRC: 82.9%-90.1% Adenoma: 45.5%-57.2%	CRC: 81.3%-94.8% Adenoma: 61.7%-85.4%	No data	CRC: 93.9%-99.1% Adenoma: 89%-94%	CRC or advanced adenoma: 74%
FN rate	No data	No data	No data	No data	No data	No data	No data	No data

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3.4.2 Evidence tables

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Lieberman 2000	Colonoscopy	Cross-sectional survey:	Randomly selected average risk asymptomatic 50-75 years old men referred for CRC screening at 13 VA medical centres. N. 3196 USA	Positive results: polyp or mass (Q 4) % cancer or adenoma (Q 3) Complication of colonoscopy (Q 8) Incomplete examination (Q9-Q10) Stage I,II (Q6)	Q 4: positive rates: 53.8% Q 3: cancer or adenomas : any adenoma or cancer: 37.5%; advanced neoplasia: 10.5% Q 8 complication of colonoscopy: 0.3% Q 9-10: 2.3% Q 6:stage I,II:73.3% Distal colon defined as rectum , sigmoid and descending: Advanced disease in the distal: 7.3% Advanced disease in the proximal: 4.1% Distal colon defined as rectum and sigmoid: Advanced disease in the distal: 6% Advanced disease in the proximal: 5.4% Patient with advanced lesion only in the proximal colon: 2.7%	**V** If FS had been be performed examining colon until the splenic flexure followed by colonoscopy if adenoma had been found, 79.9% of advanced neoplasia would have been identified. If FS had been performed only until the junction of the descending colon to the sigmoid, 68.1% of advanced neoplasia would have been identified. Authors underline that their sample included a dispporportionately high number of patients with family history of CRC

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
NORCCAP study 2003	1.one only FS 2. once only FS + FOBT immunochemical	RCT	Random sample of general population aged 55-64 years n. 20003 Norway	Positive results: polyp or mass (Q 4) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3) PPV (Q 7) FN rate (Q 19)	Q 2: compliance: FS +FOBT arm: 63% FS only arm: 67% Q 4: positive rates: FOBT: 5.6% both FOBT and FS positives: 1.6% FS negative, FOBT positive: 3.2% FS positive, FOBT negative: 12.9% All FS : 20.4% Q7: positive predictive value: both FOBT and FS positives: 64%% FS negative, FOBT positive: 5.9% FS positive, FOBT negative: 9.7% FOBT: 26% Q 19 :false negative rate: FOBT: 74% Q 5 further investigation: 19.5% Q 3: cancer or adenomas: any neoplasia FS +FOBT arm: 11% FS only arm: 12% detection rate for cancer: 3.2/1000	II

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome and the other outcomes are related to test performance; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is not feasible for the kind of intervention compared .

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Weissfeld 2005 PLCO	Flexible sigmoidiscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of RCT PLCO	Random sample of general population aged 55-74 years n. 77465 USA	Positive results: polyp or mass (Q 4) Inadequate test (Q 9) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3) % with stage I,II (Q 6)	Q 2: compliance: 83.5% Q 4: positive rates: 23.4% Q 9 inadequate test: 11% Q 5 further investigation: 74.2% of positives; 17.3% of the all sample Q 3: any cancer or adenomas: 52.2% of further investigation; 9% of the all sample; advanced neoplasia: 4.47% detection rate for cancer: 2.9/1000 Q 6: stage I : 58.6% stage II: 18.3% of people with cancer Complication of FS and colonoscopy not reported	**V** Authors underline that the compliance was high

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
UK FS screening trial Investigators	Flexible sigmoidoscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of multicentre RCT in UK	Random sample of general population aged 55-64 years n. 57254 UK	Positive results: polyp or mass (Q 4) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3) % with stage I,II (Q 6) Complication of colonoscopy (Q 8) Complication of FS (Q 21)	Q 2: compliance: 71% Q 4: positive rates: 27.7% Q 5 further investigation: 5.3% of the all sample Q 3: Any adenoma or cancer:12.4%; advanced neoplasia: 5%; detection rate for cancer: 3.5/1000 Q 6: Dukes A: 62% of cancers Dukes A or B: 74% Q 8: complication of colonoscopy: 0.5% Q 21: complication of sigmoidoscopy: 1 perforation in 40332 people who ha FS. 12 patients admitted to hospital for bleeding. Overall complication rate: 0.03%	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2005 (SCORE 2)	1.biennial immunogic FOBT delivered by mail 2. biennial immunogic FOBT delivered by GP 3 once only sigmoidoscopy 4. FS followed by biennial FOBT 5 patient choice between once only FS and FOBT	Multicentre RCT	Random sample of general population aged 55-64 years n. 26682 Italy	Positive results: polyp or mass (Q 4) Inadequate test (Q 9) Incomplete test (Q 10) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3) Adverse effect of colonoscopy (Q 8) Complication of sigmoidiscopy (Q 21) Adverse events of FOBT (FP rate, FN rate) (Q20)	Q 2: compliance: FOBT (1+2): 28.6% FS (3+4): 28.1% Patient choice (5): 27.1% (14.6% FOBT, 12.5 % FS) Q 4: positive rates: FOBT (1+2+5): 4.3% FS (3+4+5): 18.6% Q 5 further investigation FOBT (1+2+5): 4.3%; 87.7% of positives accepted FS (3+4+5):7.6% of the all sample Q 3: cancer or adenomas: FOBT (1+2): 1.8% cancer detection 3.4/1000 FS (3+4+5): 5.1% cancer detection rate:3.5/1000 Q7: positive predictive value: FOBT:45.8% of the colonoscopy performed; 40% of the positives FS: 6. 7% Q 9 inadequate test FS(3+4+5): 8.1% (FS) Q 10 incomplete test FOBT (1+2+5):23.3% (colonoscopy) FS(3+4+5):12.9%(FS) FS(3+4+5)::13% (colonoscopy) Q 8 adverse effecto of colonoscopy: 0.3%: Minor self limited complication: 3.9% Q 21: complication of sigmoidoscopy: 1case of severe vagal reaction and apparent cardiac arrest. Minor self limited complication: 0.5% Q11-Q12: malignant lesion referred to surgery: 0.1% referred straight to surgery after FS (counted on the all sample); 7.6% after colonosocopy (counted on people who had colonoscopy) Q 20 FP and FN rate of immunological test. : FP: 54%	II Participation to a mass screening in Italy would not be different if FOBT or FS had offered. The detection rate of advanced neoplasia was statistically significantly higher for FS than for FOBT. A limitation of the study is that it compare only round of FOBT vs FS.

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is feasible for the kind of intervention compared;

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2007 (SCORE 3)	1.biennial immunogic FOBT (FIT) 2. once only colonoscopy 3.once only signoidoscopy	Multicentre RCT	Random sample of general population aged 55-64 years n. 18477 Italy	Positive results: polyp or mass (Q 4) Inadequate test (Q 9) Incomplete test (Q 10) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3)	Q 2: compliance: Fit: 32.3% FS: 32.3% Colonoscopy :26.5% Q 4: positive rates: Fit: 4.7% FS: 18.9% Colonoscopy :31.1% Q 5 further investigation Fit:4.7%; 88% accepted FS: 7.2% 89.9% accepted Q 3: cancer or adenomas: Fit: 1.2% FS: 11.8% Colonoscopy :18% Q7: positive predictive value for advanced neoplasia: FIT: 28.4% (counted on the n. of CT performed); FS: 6.2% (counted n the n. of positive results) Q 20: FP rate: 71.6% Q 9 inadequate test FS: 1.1% Colonoscopy: 2.1% Q 10 incomplete test Colonoscopy: 13,2% Comparison of advanced neoplasia yeld colonoscopy vs FS: 42% of increase, explained by a marker increase of DR in people aged 60 and over. DR for distal neoplasia: no difference between FS and colonoscopy :OR: 1.02 (CI95% 0.75-1.47) FIT vs FS: marker lower DR of advanced neoplasia: OR 0.22 (CI95% 0.14-0.35)	II Authors concluded that their findings are consistent with previous studies which estimated that FS might detect 70% of the advanced neoplasms detected by colonoscopy and approximately 25% of proximal neoplasms. Authors concluded that their findings support the hypothesis that FS may represent and efficient screening strategy for average risk people before age 60 years

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is feasible for the kind of intervention compared;

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2007 (SCORE)	.once only signoidoscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of RCT SCORE	Random sample of general population aged 55-64 years n. 17148 Italy	Positive results: polyp or mass (Q 4) Inadequate test (Q 9) Incomplete test (Q 10) Compliance (Q 2) % with further investigation (Q 5) % cancer or adenoma (Q 3) Complication of colonoscopy (Q 8) % with stage I,II (Q 6) Complication of sigmoidiscopy (Q 21)	Q 2: compliance: 58.3% Q 4: positive rates:17.6% Q 5 further investigation: 8.3% Q 3: cancer or adenomas:11.3%; detection rate for cancer: 5.4/1000 Q 9 inadequate test:12.7% Q 10 incomplete test:7.5% Q 8: complication of colonoscopy:1.2%: minor self limited complication: 4% Q 6: Dukes A:54% Q11-Q12: malignant lesion referred to surgery: 0.2% referred straight to surgery after FS (counted on the all sample); 4.5% after colonosocopy (counted on people who had colonoscopy) Q 21: complication of sigmoidoscopy: 1 perforation in 9911 people who had FS; overall complication rate: 0.02% Minor self limited complication: 0.6%	V FS is generally acceptable and safe

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Regula 2006	colonoscopy	Cross-sectional survey:	Randomly selected average risk asymptomatic 40-66 years old men referred for CRC screening. People 40-49 years included if they had family history of cancer of any type N. 50148 Poland	Positive results: polyp or mass (Q 4) % cancer or adenoma (Q 3) Complication of colonoscopy (Q 8) Incomplete examination (Q9-Q10) Stage I,II (Q6)	Results of the 50-66 years old at average risk Q 4: positive rates: 25% Q 3: cancer or adenomas: any adenoma or cancer: 14.9%; advanced neoplasia 6.8% Q 8 complication of colonoscopy: 0.1% Q 9-10: 8.9% Q 6:stage I,II:62.5% Number needed to screen to detect advanced neoplasia 50-54 years Men: 18 (CI95% 16-20) Women: 31 (CI95%28-35) 50-59 years Men: 12 (CI95%11-14) Women: 23 (CI95%21-26) 60-66 years Men: 10 (CI95% 10-11) Women: 19 (CI95% 17-21)	**V** data suggest that a national program of screening colonoscopy is feasible. Bowel preparation was sufficiently good for 91.9% of participants and sedation was necessary only for the 29.8%. Authors underline that they analysed only data of participants who agreed to participate

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schoenfeld 2005	Colonoscopy	Cross-sectional survey	Consecutive average risk asymptomatic 50-79 years old women referred for CRC screening at four military centres . n. 1539 USA	Positive results: polyp or mass (Q 4) Compliance (Q 2) % cancer or adenoma (Q 3) Complication of colonoscopy (Q 8) Incomplete examination (Q9-Q10)	Q 2: compliance: 93.1% Q 4: positive rates: 20.4% Q 3: cancer or adenomas: any adenomas or cancer: 20.4%; advanced neoplasia: 4.9% Q 8 complication of colonoscopy: 0% Q 9-10: 1.3% If only FS had been performed advanced colorectal neoplasia have been identified in 1.7% and missed in 3.2% of participants. 34./% of advanced neoplasia would have been identified by FS alone. If distal colon is defined as rectum and sigmoid 94% of advanced neoplasia would have been missed. If distal colon is defines as rectum, sigmoid and descending and FS would have been performed to the splenic flexure, 92.3% of advanced neoplasia would have been missed.	V colonoscopy is the preferred method of screening for CRC in women and that FS is an adequate method for detecting advanced neoplasia in the proximal colon in women. A comparison with the findings of VA Cooperative Study 380 in men indicate that the diagnostic yeld of FS is significantly lower among 50-59 years old women than among men, although advanced neoplasia is less common in women than in men.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Results	Level of evidence
UK CRC Pilot Group 2004	FOBT GUAIAC test	Demonstration pilot study. Cross-sectional survey	478250 residents in England and Scotland aged 50-69 years. People received the kit by post from central office	Compliance (Q 2) Positivity rates (Q 4) incomplete colonoscopies /sigmoidoscopies (Q 10) colonoscopy uptake (Q 5) detection rates (cancers and adenomas) (Q 3) proportion of screen detected cancers are TNM stage I or II (Q 6) PPV of screening test (Q 7) false positive rate (Q 19) complication of colonoscopy: (Q 8)	Results are reported in the table "fobt rct table"	V

Reference: UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. BMJ 2004;329:133

3.5   Additional evidence table prepared after December 2009

1.   Brenner H, Hoffmeister M, Brenner G, Altenhofen L & Haug U (2009), Expected reduction of colorectal cancer incidence within 8 years after introduction of the German screening colonoscopy programme: estimates based on 1,875,708 screening colonoscopies, *Eur.J.Cancer*, vol. 45, no. 11, pp. 2027-2033.

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Brenner 2009	Patients with a first screening colonoscopy from age 55 on, and a second screening colonoscopy after 10 or more years, provided the first screening colonoscopy was performed before the age of 65	to estimate the reduction in case numbers and incidence of CRC by detection and removal of advanced adenomas at first round screening colonoscopy between 2003 and 2010, i.e. within the initial 8 years after implementation of the screening programme. Cross-sectional study	1,875,708 women and men included in the national screening colonoscopy programme	Detection rate of advanced adenoma	detection rate of advanced adenomas of 7.5-8.6% in men and 4.4-4.9% in women	V

4
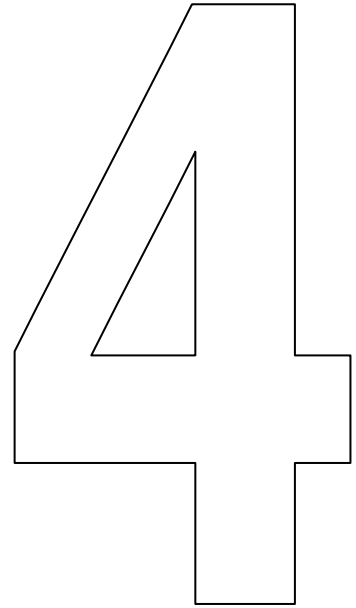
Faecal Occult Blood Testing EVIDENCE

EU CRC Guidelines Literature Group

4.1 Effect of different sampling techniques on FOBT screening uptake and/or compliance

4.1.1 Summary document

Rita Banzi

CLINICAL QUESTION 1

Do different sampling techniques change FOBT screening uptake and/or compliance?

PICOS

P: Asymptomatic population eligible for population colorectal screening
I: Stool collection by spatula, brush, stick etc.
C: Different sampling techniques
O: Uptake/Compliance
S: Systematic reviews, RCTs, observational studies

SEARCH METHOD

We searched <u>MedLine</u> and <u>Embase</u> databases from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*)
AND
(patient participation OR patient attendance OR patient response OR patient adherence OR patient choice* OR "Patient Acceptance of Health Care"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Patient Compliance"[Mesh])
We limited our search to articles published in English, Italian, French, and Spanish.
We also searched the Cochrane Library.
After merging of outputs, abstract were screened for questions 1 and 2: 30 records were considered possibly relevant for question 1 and the corresponded full texts were retrieved.

RESULTS

We found one RCT (1) addressing the issue that different sampling techniques can change FOBT screening compliance, and two cross-sectional studies (2,3) which reported information on preference among different types of stool sampling methods. A well-designed RCT conducted in Australia on 1,818 urban residents aged 50-69 years extracted from the electoral roll compared the participation rate of three screening cohorts(1). The invited population was randomised to use a wooden spatula sampling (Hemoccult SENSA kit), a spatula sampling (FlexSure, three samples), and brushing of the surface of stools method (InSure, two samples). These methods also differ regarding the need of drug and dietary restriction (only patients randomised to Hemoccult SENSA group were asked to avoid red meat, uncooked or lightly cooked turnips, horseradish, broccoli, radishes and cauliflower, vitamin C

supplements, aspirin, and nonsteroidal anti-inflammatory drugs at least 72 hours before and during sample collection). The overall participation rate was significantly higher in the InSure group (Hemoccult SENSA: 23.4%, FlexSure: 30.5%, InSure: 39.6% χ2=37.1, p<0.00001). A simplified sampling of stools using a brush was associated with a significant increase in screening participation (InSure: 39.6% FlexSure OBT: 30.5%, χ2=10.6, p=0.002).

In a British cross-sectional study (2) 1,318 (50%) of the eligible population (n = 2,639) registered with two general practices in South Birmingham were randomly selected and sent a 3-page questionnaire aimed at assessing the perceived acceptability of three potential methods of FOBT sampling: **Sterile transport swab** (requiring a small sample of faecal material to be extracted from the motion using a long stick (like a cotton bud), which is then sealed in a plastic test tube);
Smear card (requiring a small sample of faecal material to be smeared on a card using a stick)
Faecal specimen pot (requiring extracting a sample of faecal material from the motion into a pot using a scoop). A sterile transport swab was reported to be the preferred method of sampling and the smear card that will be used in the UK national screening roll-out was the least preferred method.

Finally, a small cross-sectional study aimed at determining if subjects find alternate stool collection methods (toilet tissue smear and direct smear) preferable to the use of the traditional wooden stick provided with the Hemoccult test failed to show a statistical difference (p=0.05)(3).

CONCLUSIONS

No clear recommendation is possible on which sampling technique achieves a better FOBT screening uptake and/or compliance. Only one well-designed RCT was retrieved which showed that inconvenience of dietary and drug restrictions and aversion to sampling faeces are two significant barriers to participation in screening for colorectal cancer. The best improvement in participation is achieved using a brush-sampling faecal immunochemical test for haemoglobin, as it addresses both sampling and dietary restriction barriers (LEVEL OF EVIDENCE II). One cross-sectional survey on 1318 participants showed that a sterile transport swab was the preferred method of sampling compared to smear card and faecal specimen pot (LEVEL OF EVIDENCE V).

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2. Ellis RJ, Wilson S, Holder RL & McManus RJ (2007), Different faecal sampling methods alter the acceptability of faecal occult blood testing: a cross-sectional community survey, *Eur.J.Cancer*, vol. 43, no. 9, pp. 1437-1444.

3. Greenwald B (2006), A pilot study evaluating two alternate methods of stool collection for the faecal occult blood test, *Medsurg.Nurs.*, vol. 15, no. 2, pp. 89-94.

4.1.2   Evidence tables

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Cole 2003	RCT	Three cohorts **Hemoccult SENSA**: Invitees were asked to use the manufacturer's wooden spatula to sample each of three stools (two windows from each), keeping the stool clear of toilet bowl water using a paper "raft" (provided) so as to reduce leaching of haem from the surface. Dietary restriction requested. **FlexSure**: Invitees were asked to sample each of three stools (one card per stool) using a spatula similar to that for Hemoccult, keeping the stool clear of toilet bowl without dietary restriction **InSure**: The invitee is asked to sample the stool by briefly brushing the surface of the stool while immersed in toilet bowl water.; only two samples; without dietary restriction	1818 urban residents 50-69 years randomly extracted from the electoral roll Australia	12 weeks	Changes in participation rate according to _Presence or not of dietary and drug restriction _Different sampling methods _Both the above mentioned factors _Demographic variables and socio-economic status	***Overall participation rate*** Hemoccult SENSA: 23.4%, FlexSure: 30.5% InSure: 39.6% $\chi2=37.1$, p<0.00001 ***Effect of elimination drugs and dietary restrictions*** FlexSure OBT: (without dietary restriction)30.5% Hemoccult SENSA (with dietary restriction): 23.4% $\chi2=7.39$, p=0.007 ***Effect of simplified stool sampling*** InSure: 39.6% (simplified stool sampling) FlexSure OBT: 30.5%, $\chi2=10.6$, p=0.002 ***Effect of combining simplified stool sampling with elimination of diet and drug restrictions*** InSure: 39.6% Hemoccult SENSA: 23.4% $\chi2=36.0$, p<0.001 A non significant trend to better participation from women and those aged 60–69 years, and a statistically significant trend towards higher participation for those residing in the higher socioeconomic area (p=0.047).	**II** Inconvenience of dietary and drug restrictions and aversion to sampling faeces are two significant barriers to participation in screening for colorectal cancer. The best improvement in participation is achieved using a brush-sampling faecal immunochemical test for haemoglobin, as it addresses both barriers.

Quality assessment: adequate randomisation and adequate concealment of allocation: the 4000 invites were assigned a random number using the random number function of the software program Excel (Microsoft, USA). These were ranked in ascending order, with the corresponding individuals' names concealed. The first 606 were allocated to the Hemoccult group, the second 606 to the FlexSure OBT group and the third 606 to the InSure group. There were no exclusions. Protection against contamination: it is unlikely that the control received the intervention; Intention to treat analysis. Blinded assessment of outcomes.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Ellis 2007	Cross-sectional study	Postal questionnaire assessing the perceived acceptability of three potential methods of FOBT sampling: **Sterile transport swab** (requiring a small sample of faecal material to be extracted from the motion using a long stick (like a cotton bud), which is then sealed in a plastic test tube) **Smear card** (requiring a small sample of faecal material to be smeared on a card using a stick) **Faecal specimen pot** (requiring extracting a sample of faecal material from the motion into a pot using a scoop)	1,318 (50%) of the eligible population (n = 2,639) registered with two general practices in the South Birmingham randomly selected and sent a three page questionnaire aged 50–69 UK	Not applicable	Acceptability of FOBT measured by a mean score on a five-point Likert acceptability scale (from 1: 'very acceptable' to 5: 'very unacceptable')	***Overall acceptability of FOBT*** 94.5% rated the FOBT very acceptable or acceptable ***Acceptability of the FOBT sampling methods (mean score on a five-point Likert acceptability scale)*** General FOB: 1.56 Sterile transport swab: 1.72 Smear card: 2.36 Faecal specimen pot: 2.36 When asked to specify which one of the three methods was best, the sterile transport swab was rated the highest (55.9%), followed by the faecal specimen pot (22.2%) and the smear card (7.1%)	**V** In this survey, most participants (94.5%) rated FOBT as a general concept as 'very acceptable' or 'acceptable'. However, when sampling methods were described, the acceptability rates fell and significant differences between the mean scores for each method were observed. A sterile transport swab was reported to be the preferred method of sampling and the smear card that will be used in the national screening roll-out was the least preferred method. The observed association between the acceptability of FOBT and different sampling methods could be related to the unpleasantness of sampling.

Quality assessment: 20 exclusions at the beginning of the survey (reasons fully reported). The study had a response rate of 63.2% (820/1298)

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Greenwald 2006	Cross-sectional study	Survey on preference among different type of stool sampling methods completed by subjects after the specimen collection The three methods were: • wooden stick smear, • toilet tissue smear, and • direct smear	50 adults older than 18 year old known by the researchers (co-workers, friends, and family members) USA	Not applicable	To determine if subjects find alternate stool collection methods (toilet tissue smear and direct smear) was preferable to the use of the traditional wooden stick provided with the Hemoccult test.	***Subjects who preferred*** wooden stick collection method: 24 (51%) toilet tissue collection method: 22 (46.8%) direct smear method: 1 (2.1%) No statistical difference between subject preferences for the wooden stick and the toilet tissue smear collection methods (p=0.05). 19 subjects [(40.4%), including eight who most preferred the stick method, indicated that they would prefer the direct smear method if the collection window were larger. 43 subjects (91.5%) responded they would be more likely to complete and return the test if they were able to use their most preferred method	**V** The results of this pilot study support the use of the toilet tissue smear method equal to the traditional wooden stick method. Most subjects (n=43; 91.5%) indicated they would be more likely to complete and return the test if they could use their most preferred method. These results indicate that patients who are allowed to choose their method of stool collection may be more compliant with the FOBT.

Quality assessment: 47/50 surveys and Hemoccult test cards (94%) were returned.

4.2 Effect of different test distribution or collection on FOBT screening uptake and/or compliance

4.2.1 Summary document

Rita Banzi

CLINICAL QUESTION 2

What evidence is there that the method of test distribution/collection changes uptake/compliance?

PICOS

P: Asymptomatic population eligible for population colorectal screening
I: Methods of providing the population with test kits
C: Different methods
O: Uptake/Compliance
S: Systematic reviews, RCTs, observational studies

SEARCH METHOD

We searched MedLine and Embase databases from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*)
AND
(patient participation OR patient attendance OR patient response OR patient adherence OR patient choice* OR "Patient Acceptance of Health Care"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Patient Compliance"[Mesh])

We limited our search to articles published in English, Italian, French, and Spanish.
We also searched the Cochrane Library.
After merging of outputs, abstract were screened for question 1 and 2: 13 records were considered relevant for question 2 and the corresponded full texts were retrieved.

RESULTS

Four RCTs which examined whether different methods of FOBT distribution and promotion influence screening compliance and uptake were considered relevant for this issue (1-4).
Three out of four RCTs investigated the influence of endorsement by general practitioners (GP) or other screening facilities on FOBT screening participation and compliance. (1-3)
An RCT was conducted in Australia on 2,400 participants older than 50 years who were randomised to three groups (GP1, GP2, GP3) with increasing GP promotion of FOBT screening (1). Without previous

communication or publicity, subjects were invited to a screening by immunochemical FOBT. The GP1 group was invited without indication that their GP was involved; GP2 received an invitation indicating support from the practice; and GP3 received an invitation on practice letterhead and signed by a practice partner. The participation rate increased with the increase of GP endorsement (GP1: 32.0% (±3.7%); GP2: 38.0% (±3.9%); GP3: 40.1% (±3.9%); p=0.002).

Similarly, results were reported in an Italian study performed on 7,332 participants aged 50-75 years (2). This factorial RCT compared two FOBT techniques (guaiac FOBT and immunochemical FOBT) and two test providers (GP and hospital). GP involvement in screening promotion increased the participant's compliance when compared to hospital promotion (GP: 50.2%; Hospitals: 16.2% RR: 3.40 (95% CI 3.13-3.70)(2).

Another Italian study compared different FOBT screening strategies: FOBT kit and instruction sent by mail vs. invitation letter sent by mail and FOBT kit and instruction delivered by the general practitioner (3) The study was conducted on about 8,000 participants aged 55–64 years and reported a participation rate of 30.1% and 28.1% for the FOBT by mail group and FOBT by GP or screening facility, respectively. The study showed that when FOBT screening kit was delivered by mail there was a small but statistically significant increase in the participation rate compared to kit delivery by general practitioner or screening facilities.

The effect of different methods of increasing compliance with FOBT using mailed test kits or order cards, with or without information leaflets, was investigated in an Israeli controlled trial where subjects (N=2000) aged 50-74 years were randomly assigned to receive a test kit or a kit request card (4). Mailing an FOBT kit within the framework of a screening programme lead to a substantial increase (19.9%) in the level of compliance compared to mailing a kit request card (15.9%).

CONCLUSIONS

Retrieved evidence on which test distribution and promotion strategies can increase participation in FOBT screening was specifically related to the role of GPs. Despite slight differences in the described interventions, two RCTs were consistent in reporting that GP involvement in screening promotion increased the participants' compliance when compared to hospital promotion or no intervention, while another RCT demonstrated a similar participation rate when FOBT screening kit was delivered by mail or by the GP or screening facilities (LEVEL OF EVIDENCE: I). One RCT also reported that mailing a FOBT kit within the framework of a screening programme lead to a substantial increase in the level of compliance (LEVEL OF EVIDENCE: II).

REFERENCES

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4.2.2 Evidence tables

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Cole 2002	RCT	FOBT based screening programme for colorectal cancer. <u>central screening service invitation:</u> Bowel Health Service, Repatriation General Hospital without any indication that a GP was involved. (ER and GP1) <u>central screening service invitation</u> Bowel Health Service, Repatriation General Hospital and endorsed impersonally by the person's medical practice by simply stating that the relevant (named) practice supported this offer. (GP2) <u>relevant medical practice letterhead invitation</u>: indicating that screening was endorsed by the practice and signed by the person's GP of most recent contact. (GP3)	Random selection of three groups (GP1, GP2, GP3) from two general practices and of one group (ER) from the federal electoral roll; n=600 per group (2400) Older than 50 year old Australia	12 weeks	Participation rate (defined as the return of completed stool collection devices) according to the nature of the invitation at screening	***Participation rates according to mode of invitation with different levels of GP involvement*** GP1 (invitation from Bowel Health Service): 192/600 32.0% (±3.7%) GP2 (support from named practice): 228/600 38.0% (±3.9%) GP3 (letter from practice) 244/600 40.1% (±3.9%) p=0.002, χ2=14.67 ***Overall test positivity rate*** 4.6% Positivity rates did not differ significantly between groups	**II** Apparent advocacy of screening by a person's GP of recent contact, significantly improves participation in FOBT based screening for colorectal cancer

Quality assessment: adequate randomisation (Excel random function) and allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention; attrition bias: loss to follow up not reported; detection bias: blinding of outcome assessor: not relevant because objective outcome has been used; intention to treat analysis not performed.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Federici 2005	RCT (factorial design)	Factorial design: Two test providers • GP • Hospital and two types of tests: • guaiac • immunochemical	Random sample of general practitioner and of their patients GP 130 Patients 7332 50 –75-year-old Italy	Not reported	Completion rate	***Completion rate according to different provider*** GP: 50.2% Hospitals: 16.2% RR: 3.40 (95% CI 3.13-3.70) ***Completion rate according to different test*** guaiac: 30.4% Immunochemical: 35.8% RR: 1.20 (95% CI 1.02-1.44) (adjusted for provider)	**II** The study observed a 20% higher compliance when the immunochemical test rather than guaiac test was offered, with no effect of provider. The GP involvement in screening promotion increase the compliance when compared to hospital promotion

Quality assessment: avoidance of selection bias: inadequate allocation concealment; performance bias: not applicable; protection against contamination: it is unlikely that the control received the intervention: reviewers assured verified that cohabitants received the same test; attrition bias: percentage of participants completing the study: the participation rate is the primary outcome; detection bias: blinding of outcome assessor not feasible; intention to treat analysis performed.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results*	Level of evidence Conclusions
Segnan 2005	RCT	Five screening arms: 1) biennial FOBT kit sent by mail with instructions; 2) biennial FOBT kit delivered by general practitioner or screening facility (primary care or outpatient clinics) after receiving a letter inviting patients to contact their GP or the screening centre to obtain a kit and instructions;	28 319 subjects aged 55–64 years enrolled in five centres (four involved in the SCORE trial) General practitioner setting November 1999 through June 2001 Italy	Not reported	Participation rate Acceptability and the safety of the proposed tests to the target population, to compare the detection rates of different strategies (particularly for early-stage colorectal cancer and advanced adenomas), and to estimate their costs	*Participation rates calculated for the 26 255 subjects who received the invitation letter (attendant/invited)* FOBT by mail: 682/2266 (30.1%) FOBT by GP or screening facility: 1654/5893 (28.1%)	**II** Mail delivery of the FOBT kit was associated with a 2% absolute increase in participation rate.

* Only data related to different strategies of FOBT distribution are reported

Quality assessment: subjects were identified either through general practitioners' or population register, adequate randomisation (computer generated allocation algorithm) and allocation concealment; 26682/28319 (92%) of the invited participant were randomised (reason for exclusion not reported); performance bias and detection bias not relevant; Intention to treat analysis not performed

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Ore 2001	RCT	Control: an envelope containing an FOBT kit (Haemoccult II SENSA, three faecal samples) to be sent by mail to a central laboratory as an act of compliance. Envelopes included a letter inviting recipients to perform the test annually, a detailed explanation of how the test should be carried out, and dietary restrictions for 48 hours before test performance Intervention: An envelope containing a letter as described above, and a kit request card to be returned to the same laboratory (considered as the initial response required in this approach) which then would respond by mailing the test kit to the participants. Half of all envelopes in each of the above mentioned groups also included a leaflet describing colon cancer risk and the importance of early detection of cancer	Random sample of 1000 women and 1000 men, all aged 50-74 years and residents Israel	5 months	Compliance to FOBT assessed using a National FOBT Screening Programme Database	***Compliance with the test recommendation within 4 months*** 347/1940 (17.9%) kit receivers: 19.9% card receivers: 15.9% p=0.02 There were no significant differences in overall compliance by gender (18.0% of women versus 17.8% of men). Elderly subjects (aged 65-74) were more compliant than younger subjects (20.4% versus 15.5%). The leaflet had no observable impact overall (17.9% compliance among both leaflet receivers and non-receivers).	II Mailing a FOBT kit within the framework of a screening programme lead to a substantial increase (19.9%) in the level of compliance compared to mailing a kit request card (15.9%).

Quality assessment: no information on randomisation and concealment of allocation. Assessment of outcome performed using chart records.

4.3 Test/test kit features/laboratory testing arrangements which improve the reliability of test measurement

4.3.1 Summary document

Rita Banzi

CLINICAL QUESTION 3

What test/test kit features/laboratory testing arrangements improve the reliability of test measurement?

PICOS

P: Asymptomatic population eligible for population colorectal screening
I: Test stability, transport to lab, storage, automation, number of stool samples in guaiac or immunochemical test
C: Not applicable
O: 1. % of samples suitable for analysis; 2. accuracy and precision of measurement
S: Observational studies, systematic reviews

SEARCH METHOD

We searched MedLine and Embase databases from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (Reproducibility of results [MH] OR specimen handling [MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation [MH] OR quality assurance OR quality control).

After merging of outputs, we screened 343 records in order to select 14 studies which were retrieved as full text.

RESULTS

A regression study investigated the influence of temperature and moisture content on G-FOBT sensitivity starting from the observation that the positivity rate of Hemoccult II in a 10-year screening programme significantly changed from 1.61% in summer to 2.80% during the winter(1). No significant effect of temperature alone was observed: the positive rate decrease from 74.0% at 4°C in the presence of silica gel to 68.0% at 30°C in the presence of water (p= 0.5163). Otherwise, the decrease in positive rate due to the moisture effect was statistically significant (84.0% at 4°C and 100% humidity, 58.0% at 25°C with silica gel; p= 0.0066).

A German (2, 3) study performed on a machine processed quantitative I-FOBT aimed to evaluate the reproducibility of test-development, the effect of temperature, and duration of storage on faecal sample stability as well as the test sensitivity and specificity for neoplasia. The i-FOBT test showed that samples are stable 21 days in the refrigerator without significant degradation of the test antigen. Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day: no significant variation in measurements was observed, $F(5,20)=0.24$, $p=0.66$. Test stability calculated as the Hb content decay per day measured on 42 positive tests stored for 21 days was 0.3% ± 0.4 at 4∘C, 2.2% ± 1.7 at 20∘C, and 3.7% ± 1.8 at 28∘C, respectively.

CONCLUSIONS

While no significant effect of temperature alone was observed, there is a significant relationship between moisture content and positivity rates: moisture increases test sensitivity.

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4.3.2 Evidence tables

Author, publication year	Study design	Analysed samples	Intervention	Outcome	Results	Level of evidence Conclusions
Faure 2003	In-vitro experiment to evaluate test stability (temperature, moisture)	Temperature effect: 50 stool slides stored at 4°C in the presence of silica gel; 50 stool slides stored at 30°C in the presence of water Moisture effect: 50 stool slides stored at 4°C and 100% humidity; 50 slides stored at 25°C with silica gel France	Hemoccult II	Test Stability	Temperature effect: Positive rate (%) 4°C in the presence of silica gel: 74.0% Positive rate (%) 30°C in the presence of water: 68.0% p= 0.5163 Moisture effect: Positive rate (%) 4°C and 100% humidity: 84.0% Positive rate (%) 25°C with silica gel: 58.0% p= 0.0066	A significant decrease in the percentage of positive results in summer as compared to autumn and winter. While no significant effect of temperature alone was observed, there is a significant relationship between moisture content and positivity rates: moisture increases test sensitivity

Quality assessment: N/A

Author, publication year	Study design	Participants	Exposure	Outcome	Results	Level of evidence Conclusions
Vilkin 2005; Rozen 2006)	Diagnostic accuracy study	500 ambulatory subjects who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high risk for CRC and invited for colonoscopy 53.2% males, with a mean age of 62.1±12.6% Israel	I-FOBT desktop instruments OC-MICRO	Laboratory evaluation: test stability at different temperature, specificity and sensibility at different faecal Hb cut off Clinical Evaluation: sensitivity, specificity, PPVs	**Test reproducibility** Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day: no significant variation in measurements, $F_{(5,20)} = 0.24$, $p = 0.66$. **Test Stability** Calculated Hb decay/day (measured on 42 positive tests stored for 21 days): 0.3% ± 0.4 at 4◦C (NS), 2.2% ± 1.7 at 20◦C (NS), 3.7% ± 1.8 at 28◦C (p <0.05). **Sensitivity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 79.4% 75 ng/mL: 76.5 % 100 ng/mL: 76.5 % 125 ng/mL: 70.6 % 150 ng/mL: 70.6 % 200 ng/mL: 64.7 % **Specificity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 89.7% 75 ng/mL: 93.3% 100 ng/mL: 95.3% 125 ng/mL: 95.7% 150 ng/mL: 95.9% 200 ng/mL: 96.3% **PPV (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 36.0% 75 ng/mL: 45.6% 100 ng/mL: 54.2% 125 ng/mL: 54.5% 150 ng/mL: 55.8% 200 ng/mL: 56.4%	**III** Prepared I-FOBT samples could be stored for 2-3 weeks in refrigerator without significant degradation of the test antigen. The clinical evaluation demonstrated that the recommended 100 ng/mL faecal Hb threshold guarantees the optimal sensitivity/specificity balance

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, central processing of samples, tests performed according to manufacturer instructions, no information on the blinded assessment of results.

*Significant neoplasia: CRC+Advanced adenomas polyps.

4.4 Laboratory quality assurance/external quality assessment/quality internal control procedures in the literature

4.4.1 Summary document

Rita Banzi

CLINICAL QUESTION 4

What laboratory quality assurance/external Quality assessment/quality internal control procedures have been described in the literature?

PICOS

P: Asymptomatic population eligible for population colorectal screening
I: Training, Internal QC, External QA, eye sight checks
C: Not applicable
O: Improvement of the accuracy of measurement
S: Observational studies, systematic reviews

SEARCH METHOD

We searched MedLine and Embase databases from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (Reproducibility of results [MH] OR specimen handling [MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation [MH] OR quality assurance OR quality control)

We limited our search to articles published in English, Italian, French, and Spanish.

RESULTS

After merging of outputs, we screened 343 records and we were not able to find studies reporting relevant information on the FOBT quality assurance/external Quality assessment/quality internal control procedures.

CONCLUSIONS

We found no evidence on quality assurance/external Quality assessment/quality internal control procedures on FOBT screening.

4.4.2 Evidence tables

No evidence available, see conclusions on previous page.

4.5 Impact of different testing algorithms on clinical performance

4.5.1 Summary document

Rita Banzi

CLINICAL QUESTION 5

What is the impact on clinical performance of different testing algorithms?

PICOS

P: All asymptomatic individuals eligible for population colorectal screening.
I: Testing algorithms, No. of tests / stool; No. of stools tested. Sequential (repeated) tests.
C: Different testing algorithms
O: Diagnostic accuracy (Sensitivity, Specificity, Detection Rate and PPV)
S: Observational studies, systematic reviews

SEARCH METHOD

We searched <u>MedLine</u> and <u>Embase</u> databases from 1998 using the following search strategy: (faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative* OR "False positive Reactions"[Mesh] OR "False Negative Reactions"[Mesh] OR "ROC Curve"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Sensitivity and Specificity"[Mesh])

We also searched <u>the Cochrane Library</u> and we retrieved additional studies from the analysis of literature quoted in the considered papers.

RESULTS

Sequential (repeated) test
Two consecutive diagnostic accuracy studies conducted in Scotland within the UK pilot study of screening for colorectal cancer investigated if testing individuals positive for G-FOBT in a screening programme by use of a sensitive I-FOBT could select more appropriately those who should receive colonoscopy(1, 2). In both studies the two-tier approach sensitivity was very high (95-96%) and a negative result was associated with a less than 1% chance of invasive cancer. The odds ratio for I-FOBT positive subject of being associated with cancer was 7.75 (95% CI 1.84-31.4).
A Chinese study performed on 324 subjects who underwent colonoscopy (mean age 53.5±15.3) showed that a sequential I-FOBT after a positive G-FOBT had favourable specificity for colon cancer detection over G-FOBT (94.2% vs. 75.5%), with similar sensitivity (93.8% and 95.9% vs. 95.9%, p >0.05)(3).

A multicenter diagnostic performance comparison among different FOBT tests conducted on 554 patients referred for colonoscopy (mean age 59.8±11.7) demonstrated that a combination test with a highly sensitive G-FOBT (SENSA) and an I-FOBT (FlexSure-FS or Hemeselect-HS) had slightly reduced sensitivity but significantly fewer false-positive tests than any single test. (4) The specificity of SENSA/FS (95.7%, p = 0.03) and SENSA/HS (95.2%, p = 0.07) for detection of cancer were each greater than that of any individual test.

Number of stool specimens

The previously reported Chinese study compared diagnostic performance of a 2- and a 3-sample setting approach, in which colonoscopy was offered to participants with at least one positive G-FOBT or I-FOBT result out of 2 or 3 samples respectively. I-FOBT with 2-sample testing showed compatible sensitivity and specificity to the 3-sample testing, and had a lower relative cost per cancer detected than the 3-sample testing(3).

The optimum number of times to collect stool specimens for I-FOBT was studied in a Japanese cost effectiveness analysis on 3,300 asymptomatic subjects aged over 40 years (5). The detection rate and the false-positive rate were calculated as 47% and 3.5% for the single-day method, 82% and 4.7% for the 2-day method and 88% and 5.3% for the 3-day method, respectively. This detection rate was significantly different between the single- and the 2-day methods, as well as between the single- and the 3-day methods (P<0.05). No significant differences in the false-positive rate amongst the three testing methods were observed. From the aspects of cost-effectiveness (data not reported) and diagnostic accuracy, the 2-day faecal collection method was recommended. A recent Italian multicentre study evaluated the performance of I-FOBT screening strategies according to different positivity thresholds (80, 100, 120 ng/mL) and single vs. double sampling (one, at least one, or both positive samples) using 1-day samples with cut-off at 100 ng/mL as the reference strategy. (6) A total of 20,596 subjects aged 50–69 years were enrolled from Italian population-based screening programmes. None of the screening strategies analysed in the study showed a clear-cut superiority of results. The reference strategy detected 18.4‰ significant neoplasia; the most sensitive strategy (2-day with at least one positive sample at ≥80 ng/mL) allowed for an incremental detection rate of 7.5‰, whereas the most specific strategy (2-day with both positive samples at ≥120 ng/mL) decreased the DR by 6.3‰.

CONCLUSIONS

Sequential (repeated) test

I-FOBT for individuals with positive G-FOBT could decrease substantially the number of false positives in a screening programme for colorectal cancer and could be considered when accessibility to colonoscopy is limited (LEVEL OF EVIDENCE: III).

Number of stool specimens

Few data are available on the optimal number of stool specimens to increase diagnostic performance of FOBT. One study reported that based on the analysis of costs and diagnostic accuracy the 2-day faecal collection method could be optimal but another study did not show a clear-cut superiority of the 2-day strategy (LEVEL OF EVIDENCE: III).

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4.5.2 Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results*	Level of evidence Conclusions
Fraser 2006	Diagnostic accuracy study	Evaluation of two-tier approach (sensitive I-FOBT on G-FOBT positive subjects) on the selection of population eligible to colonoscopy	1,486 G-FOBT positive invited (aged over 50-69 year old). 800 (54.0%) participate. Scotland	I-FOBT test in G-FOBT positive subjects	Diagnostic accuracy: Positive rate, sensitivity, specificity, positive and negative likelihood ratio	N/N I-FOBT: 173 (22%) N/P I-FOBT: 129 (16%) P/P I-FOBT: 498 (62%) **Number of colonoscopy:** 795/800 **Number of invasive CRC** N/N I-FOBT: 1 (<1%) N/P I-FOBT: 1 (<1%) P/P I-FOBT: 38 (8%) OR for P/P results (95% CI): 7.57 (1.84-31.4) **Number of high risk adenomatous polyps** N/N I-FOBT: 2 (1%) N/P I-FOBT: 13 (10%) P/P I-FOBT: 117 (24%) OR for P/P results (95% CI): 3.11 (1.86-5.18) **Sensitivity for CRC % (95% CI)** 95.0 (81.8-99.1) **Specificity for CRC % (95% CI)** 59.2 (36.0-43.1) **Positive likelihood ratio for CRC % (95% CI)** 1.57 (1.43-1.72) **Negative likelihood ratio for CRC % (95% CI)** 0.13 (0.03-0.49)	**III** Negative immunochemical FOBT (N/N or N/P) after a positive G-FOBT was associated with a less than 1% chance of invasive cancer

Quality assessment: prospective design, good representativeness of subjects who will received the screening, analysis of sampling bias was performed, procedures described in details, data for colonoscopy outcomes and pathology were downloaded from the appropriate screening-programme databases after completion of immunochemical FOBT analyses.

Participants were asked to send two samples of faeces from different but subsequent bowel motions: each of the two samples were scored as both samples negative (N/N), one negative and one positive (N/P), or both positive (P/P). For sensitivity, specificity and likelihood ratio were considered negative results both N/N and N/P.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Fraser 2007	Diagnostic accuracy study	To evaluate a card collection-based I-FOBT in a two tier reflex approach screening	1,124 G-FOBT positive invited (aged over 50-69 year old); 558 (49.6%) participate Scotland	card collection-based I-FOBT in G-FOBT positive subjects	Diagnostic accuracy: Positive rate, sensitivity, specificity, positive and negative likelihood ratio	Positive I-FOBT: 256 (45.9%) Negative I-FOBT: 302 (54.1%) **Number of colonoscopy:** 556/558 **Number of CRC** Positive I-FOBT: 47 (18.5%) Negative I-FOBT: 2 (0.7%) **Number of high risk adenomatous polyps** Positive I-FOBT: 54 (21.3%) Negative I-FOBT: 12 (4.0%) **Sensitivity for CRC % (95% CI)** 95.9 (84.8-99.3) **Specificity for CRC % (95% CI)** 59.2 (54.7-63.5) **Positive likelihood ratio for CRC % (95% CI)** 2.35 (2.08-2.65) **Negative likelihood ratio for CRC % (95% CI)** 0.07 (0.02-0.27)	**III** Colonoscopy revealed that this FIT was highly sensitive for colorectal cancer in this group of gFOBT-positive individuals since, of the 49 cancers found, 47 were FIT-positive and only 2 negative

Quality assessment: prospective design, good representativeness of subjects who will received the screening, analysis of sampling bias was performed, procedures described in details, no information on the blinded assessment of results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Li 2006	Cost effectiveness diagnostic accuracy study	To compare diagnostic performance of three faecal occult blood test	324 subjects underwent colonoscopy aged 53.5±15.3 years China	Guaiac based FOBT (G-FOBT) Immunochemical based FOBT (I-FOBT) Sequential FOBT (S-FOBT): I-FOBT used only as a confirmatory test for G-FOBT	Diagnostic accuracy: Sensitivity, specificity	**Number of patients with CRC** (detected by colonoscopic examination): 50/324 (15.4%) **Number of patients with adenomas** (detected by colonoscopic examination): 60/324 (18.5%) *Two-sample setting* **Sensitivity for CRC** G-FOBT: 77.5% I-FOBT: 87.8% S-FOBT: 75.5% **Specificity for CRC** G-FOBT: 88.5% I-FOBT: 96.4% S-FOBT: 98.5% *Three-sample setting* **Sensitivity for CRC** G-FOBT: 95.9% I-FOBT: 95.9% S-FOBT: 93.8 % **Specificity for CRC** G-FOBT: 75.5% I-FOBT: 89.2% S-FOBT: 94.2%	**III** I-FOBT after a positive G-FOBT had favourable specificity for colon cancer detection over G-FOBT Considering also costs (data not reported), I-FOBT with two-sample testing showed compatible sensitivity and specificity to the three-sample testing with a lower relative cost per cancer detected than the three-sample testing.

Quality assessment: N/A

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results*	Level of evidence Conclusions
Greenberg 2000	Diagnostic accuracy study	Evaluation of diagnostic performance of four different FOBT tests and two different tests combination	554 patients referred for colonoscopy (mean age 59.8±11.7) Multicenter: USA, Italy, Germany, Denmark, UK	Hemoccult II (HO) Hemoccult II Sensa (SENSA) Hemeselect (FS) FlesSure OBT (HS) SENSA+FS SENSA+ HS	Diagnostic accuracy: Positive rate, sensitivity, specificity, likelihood positive ratio	**Positivity rate (CRC)** HO: 9.4% SENSA: 11.4% FS: 15.9% (p=0.0002 vs. HO) HS: 13.5% SENSA+FS: 6.0% (p<0.05 vs. individual test) SENSA+ HS: 6.2% (p<0.05 vs. individual test) **Number of colonoscopy:** 554/554 **Number of CRC:** 16 (2.9%) **Number of high risk adenomatous polyps** 39 (7.0%) **Likelihood positive rate** Single test: 78.6%-87.5 not statistically significant SENSA+FS: 71.4% SENSA+HS: 58.3% Differences vs. individual test statistically significant **Sensitivity for CRC % (95% CI)** HO: 85.7 (90.5-95-1) SENSA: 78.6% (57.1-100.0) FS: 87.5% (71.3-100.0) HS: 83.3% (62.2-100.0) SENSA+FS: 71.4% (47.7-95.1) SENSA+ HS: 58.3% (30.4-85.2) **Specificity for CRC % (95% CI)** HO: 92.8 (90.5-95.1) SENSA: 90.5 (87.9-93.1)* FS: 86.2 (83.3-89.1)* HS: 88.2 (85.4-91.0)* SENSA+FS: 95.7 (94.0-97.4)*[#] SENSA+ HS: 95.2 (93.4-97.0)* [#] *p<0.05 vs HO [#] p<0.05 vs SENSA, FS, HS	Compared to single tests, the combination test with the highly sensitive SENSA and an immunochemical test had slightly reduced sensitivity but significantly fewer false-positive tests than any single test.

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, diagnostic procedures described in details, FOBT technicians unaware of colonoscopy results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Nakama 2000 EJC	Cost effectiveness/ Diagnostic accuracy study	To clarify the optimum number of times to collect stool specimens	3,300 asymptomatic subjects aged over 40 years Japan	Different I-FOBT (Monohaem) sampling: two days vs. one day or three days faecal sampling	Diagnostic accuracy: Positive rate, false negative and positive, detection rate	**Positive I-FOBT** Single day: 125 (3.8%), Two-days: 168 (5.1%), Three days: 191 (5.8%) **Number of patients with CRC** (detected by colonoscopic examination) Single day: 8 Two-days: 14 Three days: 15 **False negative/positive** Single day: 9; 117 Two-days: 3; 154 Three days: 2, 176 **Detection rate and the false-positive rate for CRC** Single day: 47; 3.5% Two-days: 82; 4.7% Three days: 88; 5.3% p<0.05 for detection rate between the single- and the 2-day method and between the single- and 3-day methods. No statistically significant difference for false positive rate among the three methods	**III** Considering also the cost (data not reported) the 2-day testing method can be considered the optimal immunochemical occult blood screening by Monohaem

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, procedures described in details, no information on the blinded assessment of results.

Author, publication year	Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Grazzini 2009	Prospective cohort study	20,596 subjects aged 50–69 years 53.8% women Sept 2005-June 2007 Italy	Immunochemical FOBT (latex agglutination test assay). Different screening strategies: one sample with different cut off (80, 100, 120 ng/ mL) And two samples with the same three thresholds, with at least one or both samples positive Reference strategy: 1 day with ≥ 100 ng/mL single vs. double sampling (one, at least one, or both positive samples) using 1-day sample with cut-off at 100 ng ml⁻1 as the reference strategy	Positive rate, detection rate	***Positivity rate (%)*** **<u>1 day strategy</u>** ≥ 80 ng/mL: 5.5 ≥ 100 ng/mL: 4.5 ≥ 120 ng/mL: 4.0 **<u>Difference with reference</u>** ≥ 80 ng/mL: 0.9 (95% CI 0.5; 1.4), p<0.00625 ≥ 120 ng/mL: -0.5 (95% CI -0.9; -0.1), no statistically significant **<u>2 day strategy (at least one sample positive)</u>** ≥ 80 ng/mL: 8.0 ≥ 100 ng/mL: 6.7 ≥ 120 ng/mL: 5.9 **<u>Difference with reference</u>** ≥ 80 ng/mL: 3.5 (95% CI 3.0; 3.9), p<0.00625 ≥ 100 ng/mL: 2.2 (95% CI 1.7, 2.6), p<0.00625 ≥ 120 ng/mL: 1.4 (95% CI 1.0; 1.8), p<0.00625 **<u>2 day strategy (both samples positive)</u>** ≥ 80 ng/mL: 2.8 ≥ 100 ng/mL: 2.3 ≥ 120 ng/mL: 2.0 **<u>Difference with reference</u>** ≥ 80 ng/mL: -1.7 (95% CI -2.1; -1.4), p<0.00625 ≥ 100 ng/mL: -2.2 (95% CI -2.6, -1.9), p<0.00625 ≥ 120 ng/mL: -2.5 (95% CI -2.8; -2.2), p<0.00625 ***Cancer detection rate (‰)*** **<u>1 day strategy</u>** ≥ 80 ng/mL: 2.9 ≥ 100 ng/mL: 2.8 ≥ 120 ng/mL: 2.7 **<u>Difference with reference</u>** ≥ 80 ng/mL: 0.1 (95% CI -0.9; 1.1), ≥ 120 ng/mL: -0.1 (95% CI -1.1; 1.0) none statistically significant **<u>2 day strategy (at least one sample positive)</u>** ≥ 80 ng/mL: 3.4 ≥ 100 ng/mL: 3.4 ≥ 120 ng/mL: 3.3	**III** The reference strategy detected 18.4‰ significant neoplasia; the most sensitive strategy (2-day with at least one positive sample at ≥80 ng/mL) allowed for an incremental detection rate of 7.5‰, whereas the most specific strategy (2-day with both positive samples at ≥120 ng/mL) decreased the DR by 6.3‰. None of the screening strategies analysed showed a clear-cut superiority of results

Author, publication year	Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					Difference with reference ≥ 80 ng/mL: 0.6 (95% CI -0.5; 1.7), ≥ 100 ng/mL: 0.6 (95% CI -0.5; 1.7) ≥ 120 ng/mL: 0.5 (95% CI -0.6; 1.5) none statistically significant **2 day strategy (both samples positive)** ≥ 80 ng/mL: 2.3 ≥ 100 ng/mL: 2.1 ≥ 120 ng/mL: 2.1 **Difference with reference** ≥ 80 ng/mL: -0.5 (95% CI -1.5; 0.5), ≥ 100 ng/mL: -0.6 (95% CI -1.6; 0.3) ≥ 120 ng/mL: -0.6 (95% CI -1.6; 0.3) none statistically significant *Significant neoplasia detection rate (‰)* **1 day strategy** ≥ 80 ng/mL: 20.7 ≥ 100 ng/mL: 18.4 ≥ 120 ng/mL: 17.3 **Difference with reference** ≥ 80 ng/mL: 2.3 (95% CI -0.4; 5.0), ≥ 120 ng/mL: -1.1 (95% CI -3.6; 1.5) none statistically significant **2 day strategy (at least one sample positive)** ≥ 80 ng/mL: 25.9 ≥ 100 ng/mL: 23.1 ≥ 120 ng/mL: 21.7 **Difference with reference** ≥ 80 ng/mL: 7.5 (95% CI 4.7; 10.4), p<0.00625 ≥ 100 ng/mL: 4.7 (95% CI 1.9; 7.4) p<0.00625 ≥ 120 ng/mL: 3.3 (95% CI 0.6; 6.0) not statistically significant **2 day strategy (both samples positive)** ≥ 80 ng/mL: 14.6 ≥ 100 ng/mL: 12.8 ≥ 120 ng/mL: 12.1	

Author, publication year	Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
					Difference with reference ≥ 80 ng/mL: -3.8 (95% CI -6.3; -1.3), p<0.00625 ≥ 100 ng/mL: -5.6 (95% CI -8.0; -3.2), p<0.00625 ≥ 120 ng/mL: -6.3 (95% CI -8.6; -3.0), p<0.00625 ***Number needed to scope* to find a cancer or an advanced adenoma*** Less than 2 (1.5–1.7) for the most specific strategies, whereas it was 2.4–2.7, according to different thresholds, for the most sensitive ones.	

Quality assessment: good representativeness of the population, the number needed to scope (NTS) was calculated as the number of FOBT colonoscopies needed to find one person with cancer or with significant neoplasia

4.6 Impact of rehydration of guaiac test and optimal faecal Hb cut-off limit of I-FOBT on clinical performance

4.6.1 Summary document

Rita Banzi

CLINICAL QUESTION 6

What is the impact on clinical performance of modifying the test cut-off limit?

PICOS

P: All asymptomatic individuals eligible for population colorectal screening.
I: Rehydration of guaiac test, modified cut-off limits for immunochemical tests
C: No rehydration, different cut-off
O: Accuracy and precision of measurement
S: Observational studies, systematic reviews

SEARCH METHOD

We searched <u>MedLine</u> and <u>Embase</u> databases from 1998 using the search strategies:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (Reproducibility of results [MH] OR specimen handling [MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation[MH] OR quality assurance OR quality control).

We also searched the Cochrane Library and we retrieved additional studies from the analysis of literature quoted in the considered papers.

RESULTS

Hemoccult has been compared with rehydrated Hemoccult in two large studies: in the Minnesota trial (1) as a result of rehydration, the rate of positive results increased more than fourfold, from 2.4 to 9.8%. Sensitivity increased from 80.8% to 92.2%, while both specificity and positive predictive value decreased, (specificity: 90.4%-rehydratated; 97.7%-non rehydrated. PPV: 2.2-rehydrated; 5.6-non rehydrated). In the MD Anderson study, the positivity rates were 5% and 14.6% and PPV 14% and 7%, respectively, for the non rehydrated and the rehydrated. (2)
Regarding the effect of modifying the faecal haemoglobin threshold cut-off in the immunochemical FOBT (I-FOBT) we considered data from nine studies (3-11). They all evaluated diagnostic performance of several commercially available I-FOBT systems according to different faecal haemoglobin cut off. Data are summarized in table 1. Progressively increasing the positive threshold

showed a decrease in positivity rate and test sensitivity and an increase in specificity and positive predictive values for CRC.

CONCLUSIONS

Rehydration of the Hemoccult test prior to processing can increase sensitivity and it is associated with a decrease in specificity and positive predictive value. The high positivity rate renders its value in mass screening debatable.

Considering also costs of screening and follow up (5, 7), a threshold of 100-150 ng/mL faecal haemoglobin appeared to be an optimal cut off level to guarantee an acceptable balance between sensitivity and specificity. Increasing the positivity threshold up to 300 ng/mL seems not to be advisable as the increase in specificity is too small to justify the corresponding decrease in the detection of screen positive cancers and sensitivity (LEVEL OF EVIDENCE III).

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4.6.2 Evidence tables

Table 1:

STUDY	FAECAL HB CUT OFF (NG/ML)	NAKAMA 2001 EJC JAPAN	CASTIGLIONE 2000 ITALY	CASTIGLIONE 2002 ITALY	LAUNOY 2005 FRANCE	LI-SHEN CHEN 2007 TAIWAN	ROZEN 2006 AND VILKIN 2005 ISRAEL	SIEG 1999 GERMANY	LEVI 2007 ISRAEL*
Test Positivity (%)	20	-	-	-	5.8	-	-	-	-
	50	6.5	-	-	3.1	-	-	-	-
	75	-	-	-	2.0	-	-	-	-
	100	-	3.5	4.2	-	5.5	-	-	-
	150	4.1	2.5	3.0	-	-	-	-	-
	200		2.0	2.3	-	-	-	-	-
	300	3.3	-	-	-	-	-	-	-
Test Sensitivity (%)	20	-	-		85.0	-	-	-	-
	50	89	-		68.0-83.0	81.5	79.4	-	72.5
	75	-	-		61.0-81.0	-	76.5	-	67.0
	100	-	84.0		-	81.5	76.5	-	61.5
	150	81	78.9		-	69.2	70.6	87	53.8
	200	-	73.4		-	64.6	64.7	83	-
	300	56	-		-	-	-	78	-
Test Specificity (%)	20	-	-		94.0		-	-	-
	50	94	-		97.0		89.7	-	88.6
	75	-	-		98.0		93.3	-	91.4
	100	-	97.2		-		95.3	-	93.4
	150	96	97.2		-		95.9	-	95.0
	200	-	97.2		-		96.3	-	-
	300	97	-		-		-	-	-
PPV for CRC (%)	20	-	-	-	6.0		-	-	-
	50	8.6	-	-	9.0		36.0	-	0.39
	75	-	-	-	13.0		45.6	-	0.46
	100	-	8.8	9.0	-		54.2	-	0.48
	150	12.6	11.5	11.6	-		54.5	-	0.52
	200	-	13.9	13.4	-		56.4	-	-
	300	10.8	-	-	-		-	-	-

*cancer and advanced adenoma.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Mandel 1993	Annual and Biennial Hemoccult screening groups Control group: no screening	RCT	Volunteers recruited from the American Cancer Society (and fraternal), veterans and employee groups in the Minnesota area. 46,551 subjects aged 50 to 80 years. Screening: 1975-1982, and 1986-1992	Colorectal cancer mortality reduction Number of CRC cases Number of CRC deaths Deaths from all causes Mortality reduction	13 years follow-up	**Positive rate** Rehydration: 9.8 No rehydration: 2.4 **Sensitivity** Rehydration: 92.2 No rehydration: 80.8 **Specificity** Rehydration: 90.4 No rehydration: 97.7 **Positive predictive value** Rehydration: 2.2 No rehydration: 5.6	**II** Conclusions: rehydration of specimens increased the rate of positive results more than fourfold. Both specificity and positive predictive value decrease

Quality assessment: adequate randomisation procedure, adequate allocation concealment. Individual random allocation of volunteers (stratified by age, sex and place of residence). Blinding of the participants not applicable. Analysis by intention to screen. High rate of subjects completed the offered screening (90% al least one screening). Blinded, standardised assessment of CRC mortality.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Levin 1997	Nonhydrated Hemoccult, rehydrated Hemoccult, and Hemoccult SENSA tests (SmithKline Diagnostics Inc, Palo Alto, Calif)	Diagnostic accuracy study (within a mass community-based screening study)	Asymptomatic subjects aged 50 or older 8293 kits	Diagnostic performance; participant and physician compliance	**Overall positivity rate:** 16% Rehydrated Hemoccult: 15%; Hemoccult SENSA: 7%; Nonhydrated Hemoccult: 5%. **PPV** Rehydrated Hemoccult: 7% Hemoccult SENSA: 11% Nonhydrated Hemoccult: 14%	**III** Conclusions: rehydrated Hemoccult yielded a higher positivity rate and lower positive predictive value than either Hemoccult SENSA or nonhydrated Hemoccult. Hemoccult SENSA approached the positive predictive value of nonhydrated Hemoccult.

Quality assessment: not performed (data extracted from abstract)

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Castiglione 2002	Diagnostic accuracy study (within population based screening)	To compare the diagnostic performances of different positivity thresholds in Latex agglutination test (LAT) test	19,132 aged 50-70 first attendance: 11774 subsequent attendance: 7,358 Italy	Latex agglutination test (LAT)	Positivity rates (PR), the prevalence of screen positive cancers in the population, and positive predictive values (PPVs) for CRC or for high risk adenomas	**Positive rate, % (first attendance, subsequent attendance):** LAT100: 4.2 (95% CI 3.9-4.6), 3.4 (95% CI 3.0-3.8) LAT110: 4.0(95% CI 3.6-4.3), 3.0 (95% CI 2.6-3.4) LAT120: 3.7 (95% CI 3.4-4.0), 2.8 (95% CI 2.4-3.1) LAT130: 3.5 (95% CI 3.1-3.8), 2.5 (95% CI 2.1-2.8) LAT140: 3.2 (95% CI 2.9-3.5), 2.4 (95% CI 2.0-2.7) LAT150: 3.0 (95% CI 2.7-3.3), 2.3 (95% CI 1.9-2.6) LAT160: 2.9 (95% CI 2.3-2.8), 2.0 (95% CI 1.7-2.4) LAT170: 2.7 (95% CI 2.4-3.0), 1.9 (95% CI 1.6-2.2) LAT180: 2.6 (95% CI 2.3-2.9), 1.7 (95% CI 1.4-2.0) LAT190: 2.5 (95% CI 2.2-2.7), 1.7 (95% CI 1.4-1.9) LAT200: 2.3 (95% CI 2.1-2.6), 1.65 (95% CI 1.3-1.8) **PPV for CRC** LAT100: 9.0 (95% CI 6.3-11.8), 5.5 (95% CI 2.5-8.6) LAT110: 9.7 (95% CI 6.8-12.5), 6.2 (95% CI 2.8-9.6) LAT120: 10.1 (95% CI 7.0-13.1), 6.8 (95% CI 3.1-10.5) LAT130: 10.2 (95% CI 7.1-13.4), 7.6 (95% CI 3.5-11.7) LAT140: 10.8 (95% CI 7.4-14.2), 8.1 (95% CI 3.7-12.5) **PPV for CRC (continued)** LAT150: 11.6 (95% CI 7.9-15.1), 8.5 (95% CI 3.9-13.1) LAT160: 12.1 (95% CI 8.3-15.8), 9.5 (95% CI 4.4-14.6) LAT170: 12.4 (95% CI 8.5-16.3), 9.4 (95% CI 4.1-14.7) LAT180: 12.9 (95% CI 8.9-17.0), 10.6 (95% CI 4.7-16.5) LAT190: 13.2 (95% CI 9.0-17.4), 11.2 (95% CI 5.0-17.5) LAT200: 13.4 (95% CI 9.0-17.7), 10.9 (95% CI 4.5-17.2) **PPV for high risk adenomas** LAT100: 21.3 (95% CI 17.5-25.2), 16.6 (95% CI 11.6-21.5) LAT110: 22.0 (95% CI 18.0-26.1), 16.1 (95% CI 10.9-21.2) LAT120: 22.8 (95% CI 18.6-27.0), 15.9 (95% CI 10.5-21.3)	**III** Increasing threshold from 100 to 200 ng/ml showed (a) a decrease in positivity rate; (b) a decrease in detection rates for CRC or high risk adenomas; (c) an increase in positive predictive values for cancer; (d) an increase in positive predictive value for high risk adenomas.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						LAT130: 23.9 (95% CI 19.4-28.3), 16.5 (95% CI 10.7-22.2) LAT140: 24.8 (95% CI 20.1-29.5), 17.6 (95% CI 11.4-23.7) LAT150: 26.4 (95% CI 21.4-31.4), 17.7 (95% CI 11.4-24.0) LAT160: 27.6 (95% CI 22.4-32.7), 19.0 (95% CI 12.2-25.9) LAT170: 27.6 (95% CI 21.7-32.3), 17.1 (95% CI 10.3-23.9) LAT180: 28.1 (95% CI 22.7-33.6), 17.3 (95% CI 10.0-24.6) LAT190: 28.4 (95% CI 22.8-34.0), 18.4 (95% CI 10.7-26.0) LAT200: 28.9 (95% CI 23.1-34.6), 18.5 (95% CI 10.6-26.4)	

Quality assessment: This study is part of a population screening programme. Overall the quality of the programme was acceptable (good representativeness of the population, prospective design). No information of the blinding assessment of results. In the specific special protocol: interventions details were well described according to manufacturer instructions.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Castiglione 2000	Diagnostic accuracy study (within a population based screening programme)	To compare performance of two immunochemical FOBTs: RPHA (Immudia Hem-Sp, FujiRebio, Tokyo or Hemeselect, SmithKline Diagnostics, Palo Alto) and latex quantitative test (OCHemodia, Eiken, Tokyo)	5,844 (2977 women, 2867 men) aged 50-70 Italy	RPHA vs. Hdia evaluated according to different positivity Thresholds (100 ng/mL; 150 ng/mL; 200 ng/mL)	Positivity rates (PR), the prevalence of screen positive cancers in the population, and positive predictive values (PPVs) for CRC or for high risk adenomas	**Positive tests, positive rate:** RPHA: 194, 3.3% (95% CI 2.9-3.8) Hdia 100: 206, 3.5% (95% CI 3.1-4.0) Hdia 150: 147, 2.5% (95% CI 1.5-4.3) Hdia 200: 117, 2.0% (95% CI 1.3-4.1) RPHA and Hdia200 ($p<0.00001$, df=1), RPHA and Hdia150 ($p<0.01$, df=1), Hdia100 and Hdia200, and Hdia100 and Hdia150 ($p<0.0001$, df=1) **PPV for CRC** RPHA: 10.2% (95% CI 5.6-14.8) Hdia 100: 8.8% (95% CI 4.7-12.9) Hdia 150: 11.5% (95% CI 6.1-17.0) Hdia 200: 13.9% (95% CI 7.1-20.6) No significant differences **PPV for adenomas** RPHA: 16.8% (95% CI 11.1-22.4) Hdia 100: 17.6% (95% CI12.1-23.1) Hdia 150: 22.3% (95% CI 15.2-29.5) Hdia 200: 24.8% (95% CI 16.3-33.2) No significant differences	**III** Hdia 100 was as sensitive as RPHA for cancer and high risk adenomas. Increasing the positivity threshold of Hdia up to 150 or 200 ng of haemoglobin/mg of specimen solution is not advisable as the increase in specificity is too small to justify the corresponding decrease in the detection of screen positive cancers in the population.

Quality assessment: this study is special protocol of a population screening programme. Overall the quality of the programme was acceptable (good representativeness of the population, prospective design). In the specific special protocol: both tests were applied to all the specimens, interventions details were well described according to manufacturer instructions. No information on the blinding assessment of the two series results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Li-Sheng Chen 2007	Diagnostic accuracy/ Cost effectiveness analysis Population based screening	To determine the optimal cut off of the I-FOBT	22,672 aged 50 or older (58% women) Taiwan	I-FOBT	Diagnostic accuracy: Sensitivity and false positive rates CRC or for high risk adenomas	**Positive FOBT (100 ng/mL)** 1237/22672 (5.5%) **Colonoscopy** 811 (65.6%); 276 screen-detected adenomatous polyps and 43 screen-detected CRC **Sensitivity, (95% CI) False-positive rate (95% CI) odds of being affected by positive result-OAPR (95% CI) at different cut off** 30 (ng/mL): 84.6 (73.7–91.5); 22.9 (22.4–23.4); 1:94 (1:72–1:123) 40 (ng/mL): 84.6 (73.7–91.5); 16.5 (16.1–17.0); 1:68 (1:52–1:89) 50 (ng/mL): 81.5 (70.2–89.2); 12.9 (12.5–13.4); 1:55 (1:42–1:72) 60 (ng/mL): 81.5 (70.2–89.2); 10.3 (9.9–10.7); 1:44 (1:34–1:57) 70 (ng/mL): 81.5 (70.2–89.2); 8.5 (8.2–8.9); 1:36 (1:28–1:47) 80 (ng/mL): 81.5 (70.2–89.2); 7.4 (7.0–7.7); 1:31 (1:24–1:41) 90 (ng/mL): 81.5 (70.2–89.2); 6.4 (6.1–6.8); 1:27 (1:21–1:36) 100 (ng/mL): 81.5 (70.2–89.2); 5.7 (5.4–6.0); 1:24 (1:19–1:32) 110 (ng/mL): 80.0 (68.5–88.0); 5.2 (4.9–5.5); 1:23 (1:17–1:29) 120 (ng/mL): 76.9 (65.2–85.6); 4.7 (4.4–5.0); 1:21 (1:16–1:28) 130 (ng/mL): 72.3 (60.3–81.8); 4.3 (4.1–4.6); 1:21 (1:16–1:27) 140 (ng/mL): 72.3 (60.3–81.8); 4.1 (3.8–4.3); 1:20 (1:15–1:26) 150 (ng/mL): 69.2 (57.1–79.2); 3.8 (3.5–4.0); 1:19 (1:15–1:25) 160 (ng/mL): 67.7 (55.5–77.9); 3.5 (3.3–3.8); 1:18 (1:14–1:24) 170 (ng/mL): 64.6 (52.3–75.2); 3.3 (3.1–3.5); 1:18 (1:14–1:23) 180 (ng/mL): 64.6 (52.3–75.2); 3.1 (2.9–3.4); 1:17 (1:13–1:22) 190 (ng/mL): 64.6 (52.3–75.2); 3.0 (2.8–3.2); 1:16 (1:12–1:21) 200 (ng/mL): 64.6 (52.3–75.2); 2.9 (2.6–3.1); 1:15 (1:12–1:20)	**III** Considering also the cost (data not reported) the optimal cut off for OC-Hemodia il 100 ng/mL of faecal Hb

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, procedures described in details, no information on the blinding assessment of results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Launoy 2005	Diagnostic accuracy study within a population based screening	To assess the performance of an immunochemical test with an automated reading technique (Magstream 1000)	7,421 aged 50-74 years old average risk France	I-FOBT test Magstream 1000	Diagnostic accuracy: specificity and sensibility at different faecal Hb cut off	**Positive tests**: 434 (5.8%) **Colonoscopy**: 366 (84.3%) <u>CRC</u>: 22 (6.0%) <u>adenoma ≥1 cm</u>:102 (27.9%) **Positive rate** 20 ng/mL faecal Hb: 5.8% 50 ng/mL faecal Hb: 3.1% 75 ng/mL faecal Hb: 2.0% **PPV for cancer** 20 ng/mL faecal Hb: 0.06 50 ng/mL faecal Hb: 0.48 75 ng/mL faecal Hb: 0.13 **PPV for large adenomas** 20 ng/mL faecal Hb: 0.28 50 ng/mL faecal Hb: 0.40 75 ng/mL faecal Hb: 0.41 **sensitivity for CRC at 2-year follow up** 20 ng/mL faecal Hb: 0.85 50 ng/mL faecal Hb: 0.68-0.83* 75 ng/mL faecal Hb: 0.61-0.81* **specificity** 20 ng/mL faecal Hb: 0.94 50 ng/mL faecal Hb: 0.97 75 ng/mL faecal Hb: 0.98	**III** A higher cut off is associated with a decrease in positivity rate and an increase in positive predictive value

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, central processing of samples, tests performed according to manufacturer instructions, no information on the blinded assessment of results.
* Estimated values: the first corresponds to the case where cancers not detected with a given hemoglobin content cut-off point and detected by colonoscopy at higher cut-off points had occurred within the 2 years following the test. The second value corresponds to cases that had not occurred within this period.

Author, publication year	Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Nakama 2001 EJC	Diagnostic accuracy study/Cost effectiveness analysis	4,260 asymptomatic subjects aged over 40 years Japan	Different I-FOBT cut off	Diagnostic accuracy: specificity and sensibility at different faecal Hb cut off	**Positive FOBT** 50 ng/mL faecal Hb: 278 (6.5%) 150 ng/mL faecal Hb: 175 (4.1%) 300 ng/mL faecal Hb: 139 (3.3%) **Number of CRC detected by FOBT** 50 ng/mL faecal Hb: 24/27 (88.9%) 150 ng/mL faecal Hb: 22/27 (81.5%) 300 ng/mL faecal Hb: 15/27 (55.6%) **False negative/positive** 50 ng/mL faecal Hb: 3; 254 150 ng/mL faecal Hb: 5; 153 300 ng/mL faecal Hb: 12; 124 **Sensitivity for CRC** 50 ng/mL faecal Hb: 89%; 150 ng/mL faecal Hb: 81%; 300 ng/mL faecal Hb: 56%; $p < 0.05$ for sensitivity between 50 and 300 ng/mL and 150 and 300 ng/mL; **Specificity for CRC** 50 ng/mL faecal Hb: 94% 150 ng/mL faecal Hb: 96% 300 ng/mL faecal Hb: 97% $p < 0.05$ for specificity between 50 and 300 ng/mL	**III** Considering costs (data not reported) the optimal cut off for OC-Hemodia il 150 ng/mL of faecal Hb

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, central processing of samples, tests performed according to manufacturer instructions, no information on the blinded assessment of results.

Author, publication year	Study design	Participants	Exposure	Outcome	Results	Level of evidence Conclusions
Vilkin 2005 (and Rozen 2006)	Diagnostic accuracy study	500 ambulatory subjects who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high risk for CRC and invited for colonoscopy 53.2% males, with a mean age of 62.1±12.6% Israel	I-FOBT desktop instruments OC-MICRO	Laboratory evaluation: test stability at different temperature, specificity and sensibility at different faecal Hb cut off Clinical Evaluation: sensitivity, specificity, PPVs,	**Test reproducibility** Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day: no significant variation in measurements, $F(5,20) = 0.24$, $p = 0.66$. **Test Stability** Calculated Hb decay/day (measured on 42 positive tests stored for 21 days): 0.3% ± 0.4 at 4∘C (NS), 2.2% ± 1.7 at 20∘C (NS), 3.7% ± 1.8 at 28∘C (p <0.05). **Sensitivity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 79.4% 75 ng/mL: 76.5 % 100 ng/mL: 76.5 % 125 ng/mL: 70.6 % 150 ng/mL: 70.6 % 200 ng/mL: 64.7 % **Specificity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 89.7% 75 ng/mL: 93.3% 100 ng/mL: 95.3% 125 ng/mL: 95.7% 150 ng/mL: 95.9% 200 ng/mL: 96.3% **PPV (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 36.0% 75 ng/mL: 45.6% 100 ng/mL: 54.2% 125 ng/mL: 54.5% 150 ng/mL: 55.8% 200 ng/mL: 56.4%	**III** Prepared I-FOBT samples could be stored for 2-3 weeks in refrigerator without significant degradation of the test antigen. The clinical evaluation demonstrated that the recommended 100 ng/mL faecal Hb threshold guarantees the optimal sensitivity/specificity balance

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, central processing of samples, tests performed according to manufacturer instructions, no information on the blinded assessment of results. *Significant neoplasia: CRC+Advanced adenomas polyps.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Sieg 1999	Diagnostic accuracy study (within a population based screening)	To compare immuno-chemiluminometric assay (ILMA) and standard luminescence immunoassay for Hb in feces	621 patients (280 men, 341 women; aged 15–85 years, median 59) scheduled for colonoscopy for the investigation of gastrointestinal symptoms Germany	Different I-FOBT test features	Laboratory evaluation: specificity and sensitivity at different faecal Hb cut off	**At optimal cut off (≤10 µg/g Hb; ≤2 µg/g HbHp)** **Sensitivity for CRC** Hb 87%; HbHp 83% (NS) **Sensitivity for large adenomas** Hb 54%; HbHp 73% (p<0.05) **Specificity** Hb 99%; HbHp 96% (p<0.05) **Positive test results** Hb 5% HbHp150 ng/g: 13% HbHp200 ng/g: 10% HbHp250 ng/g: 9% HbHp300 ng/g: 7% **Sensitivity for CRC and large adenoma at different cut off** HbHp150 ng/g: 87%; 76% HbHp200 ng/g : 83%; 73% HbHp250 and 300 ng/g: 78%; 65% **Specificity for CRC and large adenoma at different cut off** HbHp150 ng/g: 93% HbHp200 ng/g : 96% HbHp250 ng/g: 97% HbHp300 ng/g: 98%	**III** The sensitivity of the HbHp complex in detecting colorectal cancers to be comparable or, at higher cut-off levels, slightly below that of the Hb assay. The optimal cut-off point for HbHp complex was calculated at 200 ng/g.

Author, publication year	Study design	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Levi 2007	Diagnostic accuracy study	1,000 consecutive ambulatory symptomatic (47.1%) and asymptomatic but at increased risk for CRC (42.8%) patients who undergoing elective colonoscopy 50% men, mean age (SD), 63.2 (12.1) Israel	Immunochemical FOBT using different haemoglobin cut off and three bowel movements	Sensitivity, specificity, likelihood ratio (by the comparison with colonoscopy results)	**Colonoscopy findings** 91 patients with significant neoplasia (17 patients with cancer, 74 with at least one adenoma) **Sensitivity for detecting all clinically significant neoplasia % (95% CI)** 50-ng/mL 72.5 (63.4 to 81.7) 75-ng/mL 67.0 (57.4 to 76.7) 100-ng/mL 61.5 (51.5 to 71.5) 125-ng/mL 53.8 (43.6 to 64.1) 150-ng/mL 53.8 (43.6 to 64.1) **Specificity for detecting all clinically significant neoplasia % (95% CI)** 50-ng/mL 88.6 (86.5 to 90.6) 75-ng/mL 91.4 (89.6 to 93.2) 100-ng/mL 93.4 (91.8 to 95.0) 125-ng/mL 94.6 (93.1 to 96.1) 150-ng/mL 95 (93.6 to 96.5) **Positive and negative likelihood ratios** 50-ng/mL 6.34 (4.29-9.63); 0.31 (0.26-0.37) 75-ng/mL 7.81 (5.39-11.32); 0.36 (0.3-0.43) 100-ng/mL 9.32 (6.51-13.35); 0.41 (0.34-0.5) 125-ng/mL 9.99 (7.04-14.18); 0.49 (0.4-0.6) 150-ng/mL 10.88 (7.66-15.45); 0.49 (0.39-0.6)	**III** Using the hemoglobin threshold of 75 ng/mL or greater to define an abnormal result, the test's sensitivity was 94.1% for detecting CRC and 67.0% for detecting all clinically significant neoplasia with corresponding specificities of 87.5% and 91.4%, respectively.

Quality assessment: N/A.

4.7 Impact of diet and/or drugs on test results and/or on clinical performance

4.7.1 Summary document

CLINICAL QUESTION 7

What is the quantitative impact of diet and/or drugs on test results and/ or clinical performance?

PICOS

P: All asymptomatic individuals eligible for population colorectal screening (or in vitro studies)
I: Dietary restriction, drug restriction in G-FOBT or I-FOBT tests
C: No dietary or drug restriction
O: Test positivity, Sensitivity, Specificity, Detection Rate and PPV
S: Observational studies, systematic reviews

SEARCH METHOD

We searched <u>MedLine</u> and <u>Embase</u> databases from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative* OR "False positive Reactions"[Mesh] OR "False Negative Reactions"[Mesh] OR "ROC Curve"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Sensitivity and Specificity"[Mesh]

We also searched the Cochrane Library and we retrieved additional studies from the analysis of literature quoted in the considered papers.

RESULTS

Effect of dietary restrictions
We found one systematic review and one cohort study which assessed the impact of dietary restriction on the diagnostic performance of G-FOBT tests(1, 2). Five randomised trials, all using Guaiac-based Hemoccult tests, were included in the review. None of the included studies showed a statistically significant difference between the group in which peroxidise-containing food (red meat, no red meat, poultry, fish, or certain raw vegetables and fruits), nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), and vitamin C were prohibited compared with the group without dietary restrictions (meta-analysis: absolute difference in positivity rate: 0%; 95% CI, −1% to 1%). The cohort study conducted in Israel on 944 asymptomatic subjects attending colorectal cancer screening (mean age 60.2±11.1) reported an overall G-FOBT positivity rate of 7.5%, while neoplasia was found in 16 (22.5%) subjects with positive G-FOBT. Among subjects with and without dietary restriction the positivity rates were 7.2% and 5.5% respectively (p = 0.26).

The systematic review (1) and one subsequent RCT (3) also assessed whether dietary restriction affects G-FOBT screening completion rate. Only one study included in the systematic review (4) as well as the subsequent RCT showed a higher completion rate in the group without dietary restriction (21.4%, 95% CI 6.4-36.4; 12.6%, 95% CI 7.1-18.1).

Meta analysis for the completion rate was not performed due to high heterogeneity.

Effect of aspirin and NSAIDs

One double blind RCT and one cohort study investigated whether the use of regular aspirin or NSAIDs is a risk factor for a false-positive faecal occult blood test result. (5, 6) The RCT was conducted on healthy volunteers aged 29.8±0.6 years which were randomised to placebo, 30 mg, 81 mg, and 325 mg aspirin. A short-term (30 days) use of low-dose aspirin did not induce sufficient GI injury to cause positive faecal occult blood tests (number of GI erosion aspirin group: 6/30 (20%); placebo: 1/10 (10%) p = 0.66).

The cohort study showed no difference in the prevalence of colonoscopic findings that would potentially explain a positive faecal occult blood test result between regular aspirin or NSAID users and nonusers, even after adjusting for factors that affect the risk of a lesion that would account for a positive result (absolute difference 2% (95% CI -10-14) p=0.7). Moreover, there was no relation between the dose of aspirin and the likelihood of colonic findings (chi-squared test for trend p=0.6)

Effect of anticoagulant

The effect of medication with anticoagulant properties on the false positive rate in a population-based FOBT screening programme was evaluated in one cohort and in one case-control study (7, 8).

The cohort study conducted within the Scottish arm of the national colorectal cancer screening pilot on 846 subjects aged 50-69 years old showed that anticoagulant medication (aspirin, COX-2 inhibitors, other NSAIDs and warfarin) being taken at the time of testing is associated with an increased likelihood of a negative colonoscopy. A statistically significant 6.4% increased rate of normal examinations in those subjects on anticoagulants was observed. Diagnosis of colorectal neoplasia was higher in the no anticoagulant group compared with the anticoagulant medication cohort (56.5% vs. 47.5%; absolute difference: 9% p=0.012).

The case-control study examined all patients taking warfarin who were referred for the evaluation of a positive FOBT in an American Healthcare System programme. For each patient taking warfarin an age- and gender-matched control was enrolled. The positive predictive value of FOBT for gastrointestinal lesions consistent with occult blood loss in patients taking warfarin was similar to that in an age- and gender-matched control group of subjects with a positive FOBT who were not taking oral anticoagulants (59.0%, 95% CI, 52.3–65.8%; 53.8%, 95% CI, 47.0–60.6%; p=0.27).

CONCLUSIONS

The advice to patients to restrict their diet and avoid NSAIDs and vitamin C does not appear to change positivity rates. This finding was consistent among all studies, regardless of the intensity of the restriction. However, because a difference in the positivity rate is not a perfect indicator of differences in false positive results, it cannot be stated that dietary restriction does not improve FOBT accuracy slightly. In addition, existing trials were unable to directly measure the effect of dietary restriction on G-FOBT sensitivity. Dietary restriction, especially when particularly extensive as in the study by Robinson and colleagues (4) can slightly affect screening completion rate (LEVEL OF EVIDENCE: I, III).

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4.7.2 Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Pignone 2001	Systematic review	To evaluate the effect of diet restriction on rate of completion of FOBT and rate of positive results	Studies regarding FOBT screening which investigate the advice of dietary restrictions	All studies used G-FOBT (Hemoccult or hemoccult II) <u>Intervention group</u>: FOBT after diet restriction (defined in different terms among RCT) <u>Control</u>: FOBT	Completion rate; positive rate	**Included Studies** 5 RCTs (6576 subjects) **Completion rates** Only one study showed a higher completion rate in the group without dietary restriction. Meta analysis not performed due to high heterogeneity. **Positive rates** None of the included studies showed a statistically significant difference between the two groups. Meta analysis: absolute difference in positivity rate: 0%; 95% CI, –1% to 1%.	**I** Meta-analysis showed no difference in the positivity rate between those assigned to dietary restriction versus those not restricted.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE, HAND SEARCH OF REFERENCES OF OTHER SYSTEMATIC REVIEWS AND CLINICAL PRACTICE GUIDELINES
	Date restriction	1966/December 1999
	any restriction	Not specified
Selection	Inclusion and exclusion criteria	studies which assigned patients to dietary restriction versus no dietary restriction, reported completion rates, and used a randomised or quasi-randomised design
Validity assessment	Criteria and process used	Validity assessment of primary studies not described
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Heterogeneity of results across studies examined using the Mantel–Haenzel estimation method. Meta-analysis performed only for positive rates using the DerSimonian and Laird random-effects model.
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Rozen 1999	Cohort study	To evaluate the duration of time elapsing between preparing and developing the G-FOBT test and its effect on test positivity	944 asymptomatic subjects attending colorectal cancer screening Mean age 60.2±11.1; 54% women Israel	G-FOBT (Hemoccult Sensa) Dietary restrictions (N= 403) No-dietary restrictions (N= 541)	Positive rate	**Number of colonoscopy** 506 (53.6%) **Number of flexible sigmoidoscopy** 438 (46.4%) **Negative endoscopic examinations:** 901 **Positive rate** Overall: 71 (7.5%); Neoplasia: 16 (22.5%) Dietary restriction group: 7.2% No-dietary restrictions: 5.5% p = 0.26 **Negative rate** Overall: 873 (92.5%) Neoplasia: 27 (3.1%) Response rate of dietary compliance questionnaire: 90.8%	**III** Dietary restrictions seem not needed using Hemoccult Sensa G-FOBT

Quality assessment: the two cohorts were not simultaneously recruited; no information on the adjustment factors; blind assessment of outcome not performed.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Cole 2001	RCT	To evaluate the effect of diet restriction on screening participation	1,203 subjects aged 59-69 Diet group: 602 No-diet group: 601 Australia	Intervention group: FOBT after 72 hours of diet restriction (no read meat, uncooked turnips, broccoli, cauliflowers, rock melon, vitamin C supplements) Control: FOBT	Participation rates Positive rate	**Participation rates:** Diet group: 53.3% No-diet group: 65.9% Difference 12.6% (95% CI 7.1-18.1) Participation was significantly lower in subjects aged 50-54 years than in those aged 55-69 Diet group: p=0.03 No-diet group: p=0.009	**II** Dietary restriction has an adverse effect on participation

Quality assessment: adequate generation of the random list (random function of excel), no information on the list allocation; blinding: not applicable; adequate power calculation; unclear protection against contamination, unclear blinding of the outcome assessor, unclear evaluation of diet compliance and type of analysis (intention to screen, per protocol).

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Greenberg 1999	RCT	To examine the relationship between low-dose aspirin, GI injury at endoscopy, and faecal occult blood loss	40 healthy volunteers Mean age 29.8±0.6 years USA	Intervention: 30, 81, 325 mg Control: placebo FOBT (Hemoccult II, Hemoccult II SENSA, HemeSelect, and FlexSure OBT)	GI injury to cause positive faecal occult blood test	**GI erosion** Aspirin group: 6/30 (20%) Placebo: 1/10 (10%) p = 0.66 **Positive FOBT test** All but one participant had negative test. The only positive test was in the aspirin 325 mg group	**II** Aspirin in dosages commonly used for cardiovascular prophylaxis does not generally cause significant gastric or duodenal mucosal endoscopic lesions. Low-dose aspirin should not interfere with faecal occult blood testing and probably should not be stopped during stool collection.

Quality assessment: no information on the list generation and allocation; double blinding unclear (aspirin and placebo capsules were specially prepared for this study and were identical in appearance and taste); no information on type of analysis and power calculation;

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Kahi 2004	Cohort study	To determine whether regular use of aspirin or NSAIDs increases the risk of false-positive faecal occult blood test result	193 consecutive patients referred for a colonoscopy subjects attending colorectal cancer screening Mean age 66±10 years; 98% male USA	G-FOBT (Hemoccult II)	Type of colorectal lesion found on colonoscopy that could explain a positive FOBT result. Dose response relation between daily aspirin dose and risk of a false positive FOBT results	**Positive colonoscopy** 40 (21%) **Regular aspirin, NSAIDs, or both** 135/193 (70%) Colonic findings in people using aspirin: 29/135 (21%, 95% CI 14-28) colonic findings in people not using aspirin: 11/58 (19%, 95% CI 9-29) Absolute difference 2% (95% CI -10-14) p=0.7 No relation between the dose of aspirin and the likelihood of colonic findings (chi-squared test for trend p=0.6)	**III** No difference in the prevalence of colonoscopic findings that would potentially explain a positive faecal occult blood test result between regular aspirin or NSAID users and nonusers, even after adjusting for factors that affect the risk of a lesion that would account for a positive result (e.g., advanced colorectal neoplasia, peptic ulcer disease, and esophagitis). Aspirin and NSAID use were not risk factors for a false-positive faecal occult blood test result.

Quality assessment: prospective design, patients were blinded to study hypothesis; all endoscopists were blinded to the questionnaire and medical record findings. Power calculation reported. The use of aspirin or NSAIDs was determined by interview, medical records review, or both. Adjustment for major confounding factor.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Clarke 2006	Cohort	To evaluate the effect of medication with anticoagulant properties on the false positive rate in a population-based faecal occult blood test (FOBT) colorectal screening programme	846 subjects aged 50-69 year old 533 (63%) male UK	G-FOBT (Hema-screen)	Positive predictive value	**anticoagulant medication** 301 (35.6%) **colorectal neoplasia** anticoagulant medication: 143 (47.5%) no anticoagulant: 308 (56.5%) absolute difference: 9% p=0.012	**III** Anticoagulant medication being taken at the time of testing is associated with an increased likelihood of a negative colonoscopy.

Quality assessment: prospective design, good representativeness of subjects who will receive the screening (identification according to the general practice registration); use of anticoagulant medication assessed by interview; procedures described in details; no information on the blinded assessment of results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Bini 2005	Case control	To determine the frequency of upper and lower gastrointestinal lesions detected by endoscopy in patients taking warfarin who were referred for the evaluation of a positive FOBT and to compare these findings to age- and gender-matched control subjects with a positive FOBT who were not taking oral anticoagulants	420 referred for endoscopy after a positive FOBT older than 50 year old USA	Case: warfarin at the time of FOBT test (N=210) Control: no anticoagulant therapy (N=210)	FOBT (Hemoccult II) positive predictive value	**Gastro-intestinal lesions** Cases: 59.0% (95% CI, 52.3–65.8%) Control: 53.8% (95% CI, 47.0–60.6%) p=0.27	**IV** The positive predictive value of FOBT for gastrointestinal lesions consistent with occult blood loss in patients taking warfarin was similar to that in an age- and gender-matched control group of subjects with a positive FOBT who were not taking oral anticoagulants. These findings support continuing warfarin during FOBT.

Quality assessment: clear definition of cases and controls; adequate comparability among cases and controls (matched by age, gender); no information on the blinded assessment of outcomes.

4.8 Effect of the time between sample collection and testing and the method of storage and transport on the reliability of FOBT test and positive rate

4.8.1 Summary document

Rita Banzi

CLINICAL QUESTION 8

What is known about the effect of the time between sample collection and testing and the method of storage and transport on the reliability of the test result and the positivity rate?

PICOS

P: Asymptomatic population eligible for population colorectal screening
I: Time between collection and testing and method of storage and transport
C: Not applicable
O: Improvement of the accuracy of measurement
S: Observational studies, systematic reviews

SEARCH METHOD

We searched MedLine database from 1998 using the following search strategy:
(faecal occult blood test* OR faecal occult blood test* OR occult blood [MH] OR guaiac [MH] OR guaiac OR immunochemical test*) AND (Reproducibility of results [MH] OR specimen handling [MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation [MH] OR quality assurance OR quality control)

RESULTS

Two publications (1,2) reported the results of a German study performed on an machine processed quantitative I-FOBT aimed to evaluate the test-development reproducibility, the effect of temperature and duration of storage on faecal sample stability, and the test sensitivity and specificity for neoplasia. I-FOBT test showed that samples are stable 21 days in a refrigerator without significant degradation of the test antigen. Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day: no significant variation in measurements, $F(5,20)=0.24$, $p=0.66$, was observed. Test stability calculated as the Hb content decay per day measured on 42 positive tests stored for 21 days was 0.3% ± 0.4 at 4◦C, 2.2% ± 1.7 at 20◦C, and 3.7% ± 1.8 at 28◦C respectively.

Regarding guaiac test, we found a regression study that investigated the influence of temperature and moisture content on G-FOBT sensitivity starting from the observation that the positivity rate of Hemoccult II in a 10-year screening programme significantly changed from 1.61% in summer to

2.80% during the winter. (3) No significant effect of temperature alone was observed: the positive rate decrease from 74.0% at 4°C in the presence of silica gel to 68.0% at 30°C in the presence of water (p= 0.5163). Otherwise, the decrease in positive rate due to the moisture effect was statistically significant (84.0% at 4°C and 100% humidity, 58.0% at 25°C with silica gel; p= 0.0066).

CONCLUSIONS

Although many publications discuss the importance of the correct storage and duration of storage, we were not able to retrieve a large body of evidence on this issue. One diagnostic accuracy study concluded that prepared I-FOBT samples could be kept up to 3 weeks in the refrigeration without significant degradation of the test antigen. The time period of 2 weeks from preparation is adequate for batch processing of accumulated test samples (LEVEL OF EVIDENCE III). An in-vitro study showed that Hemoccult slides should be equilibrated in a controlled atmosphere at least 24 hours before being read (LEVEL OF EVIDENCE V).

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4.8.2   Evidence tables

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Vilkin 2005; Rozen 2006	Diagnostic accuracy study	I-FOBT desktop instruments OC-MICRO	500 ambulatory subjects who were symptomatic and scheduled for colonoscopy, or asymptomatic persons at high risk for CRC and invited for colonoscopy 53.2% males, with a mean age of 62.1±12.6% Israel	Laboratory evaluation: test stability at different temperature, specificity and sensibility at different faecal Hb cut off Clinical Evaluation: sensitivity, specificity, PPVs,	**Test reproducibility** Five prepared I-FOBT samples were quantified and repeatedly examined five more times in 1 day: no significant variation in measurements, $F(5,20) = 0.24$, $p = 0.66$. **Test Stability** Calculated Hb decay/day (measured on 42 positive tests stored for 21 days): 0.3% ± 0.4 at 4∘C (NS), 2.2% ± 1.7 at 20∘C (NS), 3.7% ± 1.8 at 28∘C (p <0.05). **Sensitivity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 79.4% 75 ng/mL: 76.5 % 100 ng/mL: 76.5 % 125 ng/mL: 70.6 % 150 ng/mL: 70.6 % 200 ng/mL: 64.7 % **Specificity (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 89.7% 75 ng/mL: 93.3% 100 ng/mL: 95.3% 125 ng/mL: 95.7% 150 ng/mL: 95.9% 200 ng/mL: 96.3% **PPV (for significant neoplasia* at different faecal Hb cut off)** 50 ng/mL: 36.0% 75 ng/mL: 45.6% 100 ng/mL: 54.2% 125 ng/mL: 54.5% 150 ng/mL: 55.8% 200 ng/mL: 56.4%	III Prepared I-FOBT samples could be stored for 2-3 weeks in refrigerator without significant degradation of the test antigen. The clinical evaluation demonstrated that the recommended 100 ng/mL faecal Hb threshold guarantees the optimal sensitivity/specificity balance

Quality assessment: prospective design, good representativeness of subjects who will receive the screening, central processing of samples, tests performed according to manufacturer instructions, no information on the blinded assessment of results.

*Significant neoplasia: CRC+Advanced adenomas polyps.

Author, publication year	Study design	Analysed samples	Intervention	Outcome	Results	Level of evidence Conclusions
Faure 2003	In-vitro experiment to evaluate test stability (temperature, moisture)	Temperature effect: 50 stool slides stored at 4°C in the presence of silica gel; 50 stool slides stored at 30°C in the presence of water Moisture effect: 50 stool slides stored at 4°C and 100% humidity; 50 slides stored at 25°C with silica gel France	G-FOBT (Hemoccult II)	Test Stability	Temperature effect: Positive rate (%) 4°C in the presence of silica gel: 74.0% Positive rate (%) 30°C in the presence of water: 68.0% p= 0.5163 Moisture effect: Positive rate (%) 4°C and 100% humidity: 84.0% Positive rate (%) 25°C with silica gel: 58.0% p= 0.0066	**V** A significant decrease in the percentage of positive results in summer as compared to autumn and winter. While no significant effect of temperature alone was observed, there is a significant relationship between moisture content and positivity rates: moisture increases test sensitivity. These results show that Hemoccult slides should be equilibrated in a controlled atmosphere at least 24 hours before being read.

Quality assessment: N/A

4.9 Additional evidence tables prepared after December 2009

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Author, publication year	Study design/ Methods	Intervention and control	Inclusion criteria	Outcome	Results	Level of evidence Conclusions
Burch 2007	Systematic review of the studies that assessed the accuracy of guaiac and immunochemical faecal occult blood tests (FOBTs) for the detection of colorectal cancer in an average-risk screening population	Guaiac and immunochemical faecal occult blood tests (G FOBT and I FOBT)	Diagnostic accuracy studies (diagnosis has not been determined prior to recruitment into the study, and all participants undergo both the index test and reference standard) comparing a guaiac and/or immunochemical FOBT with any reference standard, in an average-risk adult population and had sufficient data	Diagnostic accuracy	***Included studies*** 59 studies: 33 evaluated guaiac FOBTs, 35 immunochemical FOBTs 1 sequential FOBTs. ***Sensitivities for the detection of all neoplasms*** G FOBT 6.2% (specificity 98.0%) to 83.3% (specificity 98.4%) I FOBT 5.4% (specificity 98.5%) to 62.6% (specificity 94.3%) ***Specificity for the detection of all neoplasms*** G FOBT 65.0% (sensitivity 44.1%) to 99.0% (sensitivity 19.3%) I FOBT 89.4% (sensitivity 30.3%) to 98.5% (sensitivity 5.4%) Diagnostic case–control studies generally reported higher sensitivities.	**III** (Systematic review of diagnostic accuracy studies) Authors concluded that Immudia HemSp appeared to be the most accurate immunochemical FOBT, however, there was no clear evidence to suggest whether guaiac or immunochemical FOBTs performed better, either from direct or indirect comparisons.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	15 databases for published and unpublished studies. the internet, bibliographies of included studies and systematic reviews, key journals and conference proceedings were also searched
	Date restriction	Up to novembre 2004
	any restriction	No language restriction
Selection	Inclusion and exclusion criteria	Diagnostic cohort studies comparing a guaiac and/or immunochemical FOBT with any reference standard
Validity assessment	Criteria and process used	Validity assessment done using validated checklist: QUADAS checklist)
Data abstraction	Process used	two independent data extractors and a consensus procedure for disagreements
Quantitative data synthesis	Measures of effect, method of combining results	Sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio, with 95% confidence intervals (CIs), were calculated for each study, and results presented in ROC space. Data were not pooled where Cochrane Q was o0.0524 and/or $I2$ was >75%. Where >10 studies were included in any pooled group, regression analyses were undertaken to investigate potential sources of observed heterogeneity
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	No
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Castiglione 2007	latex agglutination test (LAT) immunochemical feacal occult blood test control: none	Diagnostic accuracy (incomplete) Ref standard: Colonoscopy recommended to FOBT-positive subjects.	27,503 subjects aged 50 – 70, living in 19 municipalities in the Province of Florence, and attending FOBT screening January 2000 to December 2002 Italy	Sensitivity (calculated by the proportional interval cancer incidence method which compares interval cancers within a given interval following a negative screening, or a positive test followed by a negative assessment, with the expected cancer incidence in the absence of screening (underlying incidence)) interval cancers being identified by linkage to the Tuscany Cancer Registry files	1- and 2-year sensitivity of LAT method	*1-year sensitivity* 80.7 (CI 95% 60.3 – 92.2) *2-year programme sensitivity* 71.5% (CI 95% 55.0 – 83.1)	**III** Authors concluded these data suggest that faecal occult blood testing Screening sensitivity may be suboptimal due to testing or programme quality problems. Increasing screening sensitivity might be achieved if the detection rate of advanced adenomas could be increased without unacceptable loss in specificity

Quality assessment: prospective recruitment; Spectrum of patients representative of the individuals who will receive the test in practice; Patients selection criteria clearly described; Verification bias: yes (colonoscopy only suggested to i-FOBT positive subjects); execution of the index test and reference standard described; Independent and blind interpretation of index test and reference standard results: no; no withdrawals from the study

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Chen 2005	Analysis of aberrant methylation of the human vimentin gene and then the assay of vimentin gene methylation as a potential marker of colon cancer in patient tumours and in faecal DNA	Intervention: vimentin gene methylation as aberrant tumour marker	Participants Normal and malignant colon tissue samples USA	Sensitivity of detecting DNA	***Sensitivity for detecting stage I and II cancers*** 43% (26 of 60 case patients) (95% CI = 31% to 57%). Only 10% (20 of 198 case patients) of control faecal DNA samples from cancer-free individuals tested positive for vimentin methylation, for a specifi city of 90% (95% CI = 85% to 94%)	**V** Authors concluded that aberrant methylation of exon-1 sequences within the nontranscribed vimentin gene is a novel molecular biomarker of colon cancer and can be successfully detected in faecal DNA to identify nearly half of individuals with colon cancer

Quality assessment: Not applicable

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Guittet 2009a	Diagnostic accuracy study (incomplete) To compare the sensitivity of the Magstream I-FOBT and the Haemoccult II G-FOBT according to the type and the location of lesions	Intervention: I-FOBT Control G-FOBT Reference standard: colonoscopy restricted to subjects classified as positive by at least one of the tests No specific dietary restriction	Participants 20,322 average-risk 50- to 74-year-old subjects underwent both tests Setting: Population screening June 2004 to 31 December 2005. France	Sensitivity of each test to detect high-risk adenomas or invasive cancers according to the location of lesions using the ratio of sensitivities (RSN)	1,277 participants had at least one positive test and a satisfactory colonoscopy result. 390 (30.5%) G-FOBT positive 1,028 (80.5%) I-FOBT positive **PPV for invasive cancers** I-FOBT 4.0% G-FOBT 6.9%; P=0.03 **PPV for high-risk adenomas** I-FOBT 24.3% G-FOBT 19.5% **Sensitivity for invasive cancer (RSN, I-FOBT/G-FOBT)** 1.48 (1.16 – 1.89) **Sensitivity for high-risk adenomas (RSN, I-FOBT/G-FOBT)** 3.32 (2.70 – 4.07) The increase in sensitivity for the detection of high-risk adenomas was significantly greater than that of invasive cancers	**III** Authors conclude that this study suggests that the gain in sensitivity by using an I-FOBT instead of a G-FOBT greatly depends on the location of lesions and the amount of bleeding. Concerning cancer, the gain seems to be confined to rectal cancer

Quality assessment: study design: prospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes: verification bias avoided: no (confirmatory procedure (colonoscopy) was restricted to subjects classified as positive by at least one of the tests) execution of index and reference tests adequately described: yes; blinding: yes (readers of the G-FOBT being blinded to the I-FOBT result); withdrawals clearly described: yes

Author, publication year	Study objective/ study design	Intervention and control	Participants/ Setting	Outcome	Results	Level of evidence Conclusions
Guittet 2009b	Diagnostic accuracy study (incomplete) To compare the performance of an I-FOBT under different positivity definitions, using the data input of two analysed samples.	Intervention: I-FOBT Control G-FOBT Reference standard: colonoscopy restricted to subjects classified as positive by at least one of the tests No specific dietary restriction	Participants 20,322 average-risk 50- to 74-year-old subjects underwent both tests Setting: Population screening June 2004 to 31 December 2005. France	Sensitivity of each test to detect high-risk adenomas or invasive cancers according to different positivity definitions (positivity threshold-varying from 20 to 150 ng/ml of haemoglobin in the buffer; number of samples performed one sample (MG 1) or two samples (MG 2); or positive test result definition when two samples were considered: at least one sample above the positivity threshold (MG 2+) or both samples above the positivity threshold (MG 2++) or mean of the two log -transformed haemoglobin contents detected by the two samples above the positivity threshold (MG 2m)) the ratio of sensitivities (RSN) was used	1,615 subjects had at least one positive test and 1,277 had a satisfactory colonoscopy 43 invasive cancers 270 high-risk adenomas Similar performance for MG 1 and MG 2+ , and improved performance for MG 2m . MG 2++ sensitivity was limited within the range of positivity thresholds evaluated. For any specificity, MG 2m provided the highest sensitivity. For any sensitivity, MG 2m provided the highest specificity. For any positivity rate, MG 2m provided both the highest sensitivity and specificity.	**III** Authors conclude that this study the replacement of MG 2+ by MG 1 or, for even better performance, by MG 2m provided that two samples are performed with similar participation (which should be explored)

Quality assessment: study design: prospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: no (confirmatory procedure (colonoscopy) was restricted to subjects classified as positive by at least one of the tests) execution of index and reference tests adequately described: yes; blinding: yes (readers of the G-FOBT being blinded to the I-FOBT result); withdrawals clearly described: yes

Author, publication year	Study design/ Methods	Intervention and control	Inclusion criteria	Outcome	Results	Level of evidence Conclusions
Haug 2005	Systematic review of to summarize pertinent studies in order to describe the current evidence for new stool tests aimed at detecting colorectal neoplasms under screening conditions.	Any new stool test suitable for population-based screening setting which might minimize the burden of colorectal cancer (CRC)	Studies reporting the examination of both cases and controls in the same study, thus allowing determination of both sensitivity and specificity. only studies with more than 10 cases and more than 10 controls were included.	Diagnostic accuracy Information relevant to practicalness and suitability for large-scale application, e.g., time limits between defecation and freezing or processing of samples and further details regarding the stool collection procedure	**Included studies** 29 studies (mostly retrospective) investigating 17 different markers or marker combinations SINGLE DNA TESTING **Detection of mutations in the proto-oncogene K-ras** Four studies Sensitivity for CRC: 40–56% **Tumour-suppressor gene APC** one study sensitivity for CRC: 61% (41-79%) sensitivity for CRC (Dukes' B2): 50% (26–74%) specificity: 95-100% **BAT26** Sensitivity for CRC (all proximal): 37% (23–52%) of CRCs none of the 69adenomas had a positive test result. Specificity was 95–100%. **SFRP2 gene** Sensitivity and specificity:77% (46–95%) COMBINATION OF TWO DNA TESTS **p53 and APC mutations** sensitivity for CRC: 88% (74–96%) specificity for CRC: 100% (78–100%) **K-ras, p53 and APC mutations** sensitivity for CRC: 91% (71–99%) sensitivity for adenomas: 82% (48–98%) (not confirmed by more recent studies)	**III** While promising performance characteristics have been reported for some tests, more pervasive evidence from larger, prospectively designed studies, which also consider aspects of practicalness, e.g., the possibility of mailing the samples, is needed

| | | | | | PROTEIN-BASED STOOL MARKERS
concentrations of decay-accelerating factor (DAF)
two studies
sensitivity for CRC to 72% (62–81%),
specificity for CRC: about 90%

calprotectin
seven studies
sensitivity for CRC: 63–90%
sensitivity for adenomas: 26–80%,
specificity: 47–76%. | |

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	Medline
	Date restriction	Up to July 2004
	any restriction	Only studies published in English
Selection	Inclusion and exclusion criteria	Studies reporting the examination of both cases and controls in the same study with more than 10 cases and 10 controls
Validity assessment	Criteria and process used	potential sources of bias was assessed, including whether sampling among cases and controls was comparable, whether analyses were performed in blinded fashion and whether bowel irritation due to recent endoscopy might have influenced the results
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Hol 2009	RCT To compare the positivity rate, detection rate and specificity of FIT (OC-Sensor micro; Eiken Chemical Co., Tokyo, Japan) screening at different cut-off levels with gFOBT (Hemoccult II; Beckman Coulter Inc., Fullerton, CA, USA) screening in an average risk screening-naive population	Intervention: I-FOBT (OC-Sensor) single faecal sample of one bowel movement without dietary restrictions or medication limitations Control G-FOBT (Hemoccult II) Three consecutive bowel movements without dietary restrictions or medication limitations.	Participants 10011 subjects aged 50 – 74 years randomly selected from the municipal registries Setting: rural and urban settings November 2006 and November 2007 The Netherlands	Positivity rate, number needed to scope (NNscope), detection rate number needed to screen (NNscreen)	**_G-FOBT (%, 95% CI)_** Positive rate: 2.8; 2.2 –3.6 PPV (advanced neoplasia): 45; 33–58 PPV (CRC): 10; 4 – 20 NNScope (advanced neoplasia): 2.2 NNScope (CRC): 10.3 Specificity (advanced neoplasia): 98.5; 97.9 –99.0 Specificity (CRC): 97.6; 94.8 – 98.9 Detection rate (advanced neoplasia): 1.2; 0.8 –1.7 Detection rate (CRC): 0.3; 0.1 – 0.6 NNscreen (advanced neoplasia): 84 NNscreen (CRC): 392 **_I-FOBT_** Positive rate: 8.1 (7.2 – 9.1)* PPV (advanced neoplasia): 42 (36 – 49) PPV (CRC): 7 (4 – 11) NNScope (advanced neoplasia): 2.4 NNScope (CRC): 14.1 Specificity (advanced neoplasia): 95.5 (94.5 –96.3) Specificity (CRC): 92.9 (88.8 – 95.5) Detection rate (advanced neoplasia): 3.2 (2.6 –3.9)* Detection rate (CRC): 0.5 (0.3 – 0.9) NNscreen (advanced neoplasia): 31 NNscreen (CRC): 186 Data for other thresholds are reported (75, 100, 125, 150, 175, 200) 62/65 (95.4%) I-FOBT-positive 226/241 (93.8%) G-FOBT-positive underwent a colonoscopy.	**II** FIT within the complete range of tested cut-off values (50–200 ng ml-1) outperforms gFOBT screening as it is associated with both higher attendance as well as higher detection rates of advanced neoplasia, even though the PPV for detecting advanced neoplasia did not differ significantly between both tests.

Quality assessment: Selection bias: sequence generation and allocation concealment adequate; Performance bias: adequate; Detection bias: not clear (blinding not reported); Attrition bias: adequate.

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Levi 2006	Diagnostic accuracy study To determine immunochemical faecal occult blood test efficacy for identifying significant neoplasia in at-risk patients undergoing elective colonoscopy	<u>Intervention:</u> I-FOBT Quantitative haemoglobin analysis performed by the OC-MICRO automated instrument using the 100 ng Hb/mL threshold to determine positivity <u>Control:</u> none	<u>Participants</u> 252 consecutive, ambulatory patients undergoing colonoscopy having a family history of colorectal cancer (CRC) non-syndromic (Lynch or polyposis) Israel	Diagnostic value of the I-FOBT for significant neoplasms (colorectal cancer-CRC or advanced adenomatous polyp-AAPs): (a) sensitivity, (b) specificity, (c) positive predictive value, (d) negative predictive value Association between medications taken and amount of faecal Hb and test positivity	CRC: 5 advanced adenoma: 14 non-advanced adenoma: 46 ***I-FOBT positivity*** 31 (12.3%) ***Diagnostic value for CRC:*** Sensitivity:100%, Specificity: 90%, PPV: 16% NPV: 100% ***Diagnostic value for all significant neoplasia:*** Sensitivity: 74%, Specificity: 93%, PPV: 45% NPV: 98% ***Saved colonoscopy*** with 88% fewer colonoscopies, all CRC and 74% of all significant neoplasia would have been identified	**III** One-time quantitative immuno-chemical determination of the faecal occult blood level would have led to the identification of 100% of CRC and 74% of all significant colorectal neoplasia, with significantly fewer colonoscopy examinations.

Quality assessment: study design: retrospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: yes; execution of index and reference tests adequately described: yes; blinding: not specified; withdrawals clearly described: yes

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Levi 2009	Diagnostic accuracy study To evaluate the effect of the use of aspirin, nonsteroidal anti-infl ammatory drugs (NSAIDS), and anticoagulants on the performance of immunochemical faecal occult blood test (I-FOBT).	Intervention: I-FOBT (≥ 75 and 100 ngHb / ml of buffer thresholds to determine positivity) Information regarding the use of medications was collected from the health medical organisation (HMO) database.	Participants 1,221 ambulatory patients having total colonoscopy after preparing three I-FOBTs. mean age was 64.0 ± 12.0 years; 616 (50.5 %) patients were men Israel	Diagnostic value of the I-FOBT for significant neoplasms (colorectal cancer-CRC or advanced adenomatous polyp-AAPs): (a) sensitivity, (b) specificity, (c) positive predictive value, (d) negative predictive value Association between medications taken and amount of faecal Hb and test positivity	CRCs: 17 (1.4 %), AAP: 97 (7.9 %) nonadvanced adenomas: 336 (27.5 %) normal colonoscopy examination 771 (63.1 %) ***Diagnostic value (≥ 75 ngHb / ml)*** ***No drug, N =980*** sensitivity: 51.20% (40.6 – 61.7) specificity: 91.20% (89.3 – 93.0) PPV: 35.80% (27.3 – 44.2) NPV: 95.10% (93.7 – 96.5) ***Aspirin, N =170*** sensitivity: 66.70% (44.9 – 88.4) specificity: 90.10% (85.4 – 94.9) PPV: 44.40% (25.7 – 63.2) NPV: 95.80% (92.5 – 99.1) ***Aspirin/NSAIDS, N =212*** sensitivity: 66.70% (46.5 – 86.8) specificity: 89.50% (85.2 – 93.9) PPV: 41.20% (24.6 – 57.7) NPV: 96.10% (93.2 – 98.9) ***Anticoagulants, N =33*** Sensitivity 87.50% (64.6 – 100) Specificity: 92.00% (81.4 – 100) PPV: 77.80% (50.6 – 100) NPV: 95.80% (87.8 – 100)	III The use of aspirin / NSAIDS and anticoagulants was associated with a trend for increased sensitivity with no change in specifi city for the detection of AAP/ CRC. This study suggests that there is no need to stop these agents before I-FOBT testing

Quality assessment: study design: prospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: yes; execution of index and reference tests adequately described: yes; blinding: not reported; withdrawals clearly described: yes

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Morikawa 2005	Diagnostic accuracy study (complete, retrospective analysis) To analyse the sensitivity of immunochemi-cal FOBT and to compare the results with the findings from complete colonoscopy	Intervention: 1-time I-FOBT Control total colonoscopy both tests done simultaneously Reference standard: colonoscopy	Participants 21,805 asymptomatic adults underwent 1-time I-FOBT and total colonoscopy simultaneously 15,694 men and 6111 women mean age of 48.2± 9.3 years (range, 20–91) Setting: Population screening April 1983 and March 2002 Japan	Sensitivity and specificity of I-FOBT	I-FOBT positivity: 1231 (5.6%) **Neoplasia** Sensitivity: 10.4 (95% CI 9.5–11.3) Specificity: 95.5 (95% CI 95.2–95.8) **Advancing neoplasia** Sensitivity: 27.1 (95% CI 23.9–30.3) Specificity: 95.1 (95% CI 94.8–95.4) **Invasive cancer** Sensitivity: 65.8 (95% CI 55.4–76.3) Specificity: 94.6 (95% CI 94.3–94.9)	**III** Although the screening of asymptomatic patients with immunochemical FOBT can identify patients with colorectal neoplasia to a certain extent, the sensitivity of 1-time immunochemical FOBT is relatively low for detecting advanced neoplasia, including CRC

Quality assessment: study design: retrospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: yes (colonoscopy performed on all the subjects); execution of index and reference tests adequately described: yes blinding: yes (endoscopists were blinded to the results of FOBT); withdrawals clearly described: yes

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Mulder 2007	Diagnostic accuracy study (complete) To compare the accuracy of faecal tumour pyruvate kinase isoenzyme type M2 (TuM2-PK) testing with immunochemical FOBT in patients with CRC or adenomas	Intervention: I-FOBT (Immo-care and OC-Light) Control TuM2-PK Reference standard: colonoscopy	Participants Patients above 18 years of age, who had an appointment for colonoscopy, were advised to provide some stool for measuring faecal TuM2-PK and immuno-chemical FOBT 181/275 patients were analysed, including 52 invasive CRC, 47 with colorectal adenomas 19 active inflammatory bowel disease (IBD) 63 matched controls with a normal colonoscopy Setting: out-clinic patients Netherlands	Specificity and sensitivity calculated using the colonoscopy results and histology as reference value	**Sensitivity for CRC (n = 52)** TuM2-PK: 85% (44/52) Immo-care: 92% (48/52) OC-Light: 94% (49/52) **Sensitivity for Adenoma (n = 47)** TuM2-PK: 28% (13/47) Immo-care: 40% (19/47) OC-Light: 34% (16/47) **Specificity** TuM2-PK: 90% (57/63) Immo-care: 97% (61/63) OC-Light: 97% (61/63)	**III** Authors conclude that both immunochemical tests performed better and showed higher sensitivities and specificities for detecting CRC than the TuM2-PK test, however, not significantly higher. No difference was observed in performance of both immunochemical tests used in this study.

Quality assessment: study design: prospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: no; verification bias avoided: yes (confirmatory procedure (colonoscopy) was restricted to subjects classified as positive by at least one of the tests) execution of index and reference tests adequately described: yes; blinding: yes (The different tests were all performed by a chemical analyst who was blinded for the results of the colonoscopy); withdrawals clearly described: yes

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion
Parekh M., 2008	To reappraise stool-based colorectal cancer screening in light of changing test performance characteristics, lower test cost and increasing colorectal cancer care costs. Cost-effectiveness analysis USA	Beginning at age 50 years, average-risk persons progress through the model for 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect US life table data	With Markov model, the study compared Faecal DNA testing every 3 years Annual FOBT or FIT And colonoscopy every 10 years.	Most cost effective strategy	**Cost effectiveness of F-DNA testing (cost/life-year gained), $** Interval: 3 vs 4 years=39200 2 vs 3 years=52600 Compared with no screening, all strategies reduced CRC incidence and mortality **Cost effectiveness** Incremental life-year gained per 100 000 person FIT vs F-DNA version 1 : 2076 FIT vs F-DNA version 1.1: 1219 FIT vs FOBT : 919 FIT vs F-DNA version2: 747 FOBT vs F-DNA version 1 : 1157 FOBT vs F-DNA version 1.1: 300 FOBT vs F-DNA version 2: 172 Incremental cost per life-year gained FIT more effective and less costly over all other strategies Faecal occult blood testing and FIT were preferred over all F-DNA versions. F-DNA version 2 vs FOBT: $ 669 000 **Sensitivity analyses** F-DNA strategies compared more favourably but still cost >$50000 As the sensitivity for large adenoma of the F-DNA version 2 test improved, this strategy became progressively more effective than FOBT. With a sensitivity for large adenoma of 80%, F-DNA version 2 cost $87 500/life-year gained compared with FOBT, but this incremental cost/life-year gained rose sharply as sensitivity for large adenoma decreased. At a test cost of $200, F-DNA version 2 cost <$50 000/life-year gained compared with FOBT when F-DNA test sensitivity for large adenoma was >60%	As novel biological therapies increase colorectal cancer treatment costs, faecal occult blood testing and faecal immunochemical testing could become cost-saving. The cost-effectiveness of faecal DNA testing compared with no screening has improved, but faecal occult blood testing and faecal immunochemical testing are preferred to faecal DNA testing when patient compliance is high. Faecal immunochemical testing may be comparable to colonoscopy every 10 years in persons adhering to yearly testing.

| | | | | | Faecal DNA testing version 2 cost $100 000 . life-year gained vs. faecal immunochemical testing when per-cycle compliance with faecal immunochemical testing was 22%.

Faecal immunochemical testing with excellent compliance was superior to colonoscopy every 10 years. | |

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Van Rossum 2009	Diagnostic accuracy study (incomplete) To evaluate the performance and efficiency of a semi-quantitative iFOBT in an average-risk screening population.	Intervention: I-FOBT (OC-Sensor) Reference standard: Colonoscopy offered to I-FOBT positive subjects	Participants 6157 subjects, 50–75 years of age, with average CRC risk Women:63% Men: 56% Setting: population-based colorectal cancer screening The Netherlands	Specificity (quite reliably estimated under the rare disease assumption as 1 minus the number of false positives relative to the total number of participants reduced by the number of true positives, disregarding the number of false FOBT-negative patients (negatives)) detection rates numbers needed to scope-reciprocal of the positive predictive value (PPV) at different cutoff levels.	**_I-FOBT positivity (≥50 ng ml-1)_** 526, 8.5% (95% CI: 7.8–9.2) colonoscopy performed on 428/526 (81%) of these patients **_overall detection rate for CRC and advanced adenomas_** ≥50 ng ml-1: 3.1% (95% CI: 2.6–3.5) ≥100 ng ml-1 2.4% (95% CI: 2.0–2.7), ≥200 ng ml-1 1.8% (95% CI: 1.5–2.2) **_NNTScope for CRC and advanced adenomas_** ≥50 ng ml-1 2.3 (95% CI: 2.2–2.3) ≥100 ng ml-1 1.9 (95% CI: 1.9–2.0) ≥200 ng ml-1 1.8 (95% CI: 1.7–1.8).	**III** Authors conclude that cutoffs below the standard 100 ng ml-1 resulted in not only higher detection rates of advanced lesions but also more colonoscopies. With sufficient capacity, 75 ng ml-1 might be advised; if not, up to 200 ng ml-1 CRC miss rates are acceptable compared with the decrease in performed colonoscopies.

Quality assessment: study design: prospective recruitment; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: no (Colonoscopy offered to I-FOBT positive subjects); execution of index and reference tests adequately described: yes blinding: no

Author, publication year	Study objective/ study design	Intervention and control	Participants/Setting	Outcome	Results	Level of evidence Conclusions
Wang, 2008	Diagnostic feasibility study (incomplete) To investigate the feasibility of detecting hypermethylated secreted frizzled-related protein 2 (SFRP2) gene in faecal DNA as a non-invasive screening tool for colorectal cancer (CRC) non-invasive screening tool for CRC.	Intervention and Reference standard: analyse SFRP2 gene promoter methylation status in a blinded fashion in tumour tissues and in stool samples taken from 69 CRC patients preoperatively and at the 9th postoperative day, 34 patients with adenoma ≥ 1 cm, 26 with hyperplastic polyp, and 30 endoscopically normal subjects.	Participants 69 patients with sporadic CRC, 60 patients with benign colorectal diseases (34 adenomas and 26 hyperplastic polyps) and 30 macroscopically normal subjects undergoing surgery and endoscopy at the First Affiliated Hospital of Yangzhou university from March 2005 to February 2007 In 69 patients with CRC: 20 <50 years old 49 >50 years old 37 male, 32 female Setting: patients undergoing surgery and endoscopy at the First Affiliated Hospital of Yangzhou	Detection rates of SFRP2 hypermethylation Sensitivities of SFRP2 hypermethylation Specificity of SFRP2 hypermethylation	Comparison of the performance characteristics of SFRP2 MethyLight assays showed that the assays could detect 92.1%, 66.7% and 71.4% of individuals with CRC, advanced adenoma and hyperplastic polyp, respectively, that carried hypermethylated SFRP2. The clinical sensitivities of SFRP2 hypermethylation in faecal DNA for detecting the presence of CRC, advanced adenoma and hyperplastic polyp were 87.0% (60/69), 61.8% (21/34) and 42.3% (11/26), respectively. To evaluate the clinical specificity of this assay, we next analysed faecal DNA of 30 normal control individuals, and found that only 2 (6.7%) samples were positive for hypermethylation of SFRP2	**III** At present, there are several methods for detecting of CRC and premalignant lesions[41,42], but none of them is really suitable for screening CRC. Our study demonstrated initially that hypermethylated SFRP2 gene in stool is a promising and noninvasive sensitive marker for screening colorectal neoplasia.

Quality assessment: study design: not clear if a prospective or retrospective recruitment has been done; spectrum of patients representative of the patients who will receive test in practice: yes; selection of patients clearly described: yes; verification bias avoided: yes; execution of index and reference tests adequately described: yes blinding: yes

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Young G.P., 2003	Two stools using a Brush-sampling test (InSure)vs three stools using traditional spatula-sampling test (FlexSure). order of sampling was randomised	To undertake a prescreening evaluation of a new brush-based faecal immunochemical test for haemoglobin, relative to a traditional spatula-sampling immunochemical test. Diagnostic accuracy study (comparative)	443 patients aged between 24 and 90 years, scheduled to undergo diagnostic colonoscopy in two major urban hospitals during January 1999 to August 2001.	Sensitivity, specificity; test preference in 46 subjects randomly selected	**Sensitivity for cancer, n positive/tot cases** InSure vs FlexSure OBT: 27/36 (75%) vs 29/36 (80.5%) Not significant different. **Sensitivity for adenomas ≥10mm, n positive/tot cases** InSure vs FlexSure OBT: 12/29 (41.4%) vs 13/29 (44.8%) Not significant different. **Sensitivity for adenomas <10mm, n positive/tot cases** InSure vs FlexSure OBT: 8/56 (14.3%) vs 8/56 (14.3%) Not significant different. **False-positive rates in normal colonoscopic diagnosis** InSure vs FlexSure OBT: 4/179 (2.2%) vs 5/179 (2.8%) (specificities of 97.8% and 97.2%, respectively). Levels of faecal haemoglobin were highest in those with cancers; those with adenomas had intermediate levels which were also significantly higher than those in normals. **Test preferences** InSure vs FlexSure OBT: 38/46 (82.6%) vs 4/46 (8.7%) (p<0.00001)	**III** In this pre-screening evaluation, the brush-sampling immunochemical technology of the InSure test is shown to be as sensitive and specific as is the FlexSure OBT for faecal globin. The novel stool-sampling method is valid, based on its ability to discriminate between normals and classes of neoplasia. Results suggest that, in the context of population screening for colorectal cancer, individuals will be more willing to perform a brush-based faecal immunochemical test than one utilising the traditional spatula method for specimen collection. If so, this should lead to better detection of neoplasia in population screening.

Quality assessment: spectrum of patients representatives of the patients who will receive the test in practice; patients selection criteria clearly described; blinded assessment of outcome: all tests were developed and interpreted by a single experienced. Colonoscopists and pathologists were unaware of the FOBT result.

5

Quality assurance in endoscopy in colorectal cancer screening and diagnosis
EVIDENCE

EU CRC Guidelines Literature Group

5.1 Adverse outcomes

5.1.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 3

Which variables, that need to be identified before the examination, are associated with an increased risk of side-effects or adverse events in FS or colonoscopy?

PICOS

P: General population at average risk of CRC (age 50 or older) and individuals with a positive FOBT/FIT
I: FS and colonoscopy
C: Not applicable
O: Bleeding, perforation, infections, pain/discomfort, completeness
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

Searches were conducted in August 2008 for primary studies on <u>MedLine</u>, <u>Embase</u> and for systematic reviews on the <u>Cochrane Library</u> including only studies published between 2000 and 2008.

<u>Pubmed</u>
The Mesh terms: (("Colonoscopy"[Mesh] AND "Risk"[Mesh]) AND "adverse effects "[Subheading]) AND "Warfarin"[Mesh] produced 2 results and one relevant paper.

The following Mesh terms produced no relevant search results:
(("Colonoscopy"[Mesh] AND "Risk"[Mesh]) AND "adverse effects ") AND "Diverticulitis"[Mesh]
(("Colonoscopy"[Mesh] AND "Risk"[Mesh]) AND "adverse effects ") AND "Heart Valves"[Mesh]
(("Colonoscopy"[Mesh] AND "Risk"[Mesh]) AND "adverse effects ") AND "Deep Sedation"[Mesh]
((("Colonoscopy"[Mesh] AND "Risk"[Mesh]) AND "adverse effects ") AND "Deep Sedation"[Mesh])
AND "Endoscopy, Gastrointestinal"[Mesh]

The following free text searches produced several papers of interest:
'colonoscopy AND female AND discomfort' produced 137 results with two papers deemed
relevant.'colonoscopy AND perforation AND risk factors' produced 79 results with two papers deemed
relevant.'colonoscopy AND warfarin AND side-effects' produced 11 results with two papers of interest.

We performed also a broader search on <u>MedLine</u> with the following strategy:
 (exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy)

Embase
The following search terms identified no relevant papers:
'colonoscopy AND adverse risks OR events AND preprocedural complications'
'colonoscopy AND adverse risks OR events AND warfarin'

The Cochrane Library
Search terms: 'preprocedural risks AND colonoscopy' identified no results.
The paper published by Garrett and Feiler 2007 was recommended by a Gastroenterologist working at St Marks Hospital, Harrow.

CLINICAL QUESTION 12

Is there evidence linking poor performance of colonoscopy with adverse outcomes for patients?

PICOS

P: General and screened populations undergoing colonoscopy
I: Colonoscopy
C: Not applicable
O: Pain and discomfort, patient satisfaction, completion rate, adverse events such as perforation and bleeding, missed colorectal cancer
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

Searches were conducted in August 2008 for primary studies on MedLine, Embase for studies published between 2000 and 2008.
Pubmed
The following Mesh terms returned no search results or results of no relevance:
 ("Evidence-Based Medicine"[Mesh] AND "Colonoscopy"[Mesh]) AND "Outcome Assessment (Health Care)"[Mesh]
("Colonoscopy"[Mesh]) AND "Pain"[Mesh]) AND "Mass Screening"[Mesh]
(("Colonoscopy"[Mesh] AND "Colorectal Neoplasms"[Mesh]) AND "Pain"[Mesh]) AND "Haemorrhage"[Mesh]
Free text search results:
'quality AND technical performance AND colonoscopy' identified 10 search results.
Embase
Search terms: 'colonoscopy AND pain AND poor performance' identified 2 search results and one paper of interest.
The paper by Bowels et al, 2004 was recommended by a Gastroenterologist at St Mark's Hospital

RESULTS

We reported the results for question 3 and 12 altogether because the results relating to these questions have been drawn from the same articles.

No relevant systematic reviews were found. We found eleven studies relevant for question three and twelve of this chapter. Six are prospective studies, three are retrospective case studies, one is a narrative review and two are cross-sectional studies.

Cross-sectional study
Eloubeidi et al, 2003 (1) examined the factors that are associated with shorter or limited screening FS. This study prospectively examined 3,980 patients. Females were twice as likely to have a procedure limited by angulation, pain or spasms. The depth of insertion of the sigmoidoscope was less in women

than in men and thus women were less likely to have their colon visualised adequately. Age, previous abdominal surgery and diverticulosis were also associated with limited examinations.

Viiala et al 2008 (2) examined the outcomes for women in an FS screening program, which were compared to men. Women found the procedure more uncomfortable (mean pain score was 2.9 for men and 4.0 for women) and have a lower insertion depth (median insertion depth for men: 60cm, women: 50 cm).

Prospective studies

Rathgaber et al 2006 (3) conducted a study of 12,407 patients and reported on completion and complication rates of colonoscopy. Failure of colonoscopy because of anatomic difficulties were more common in women than men. The authors commented that failure due to pain/discomfort in women could be related to anatomy or to visceral hypersensitivity or irritable bowel syndrome.

Bini et al, 2003 (4) evaluated complications related to endoscopy in a training setting using questionnaires. Midazolam dose (OR for each 1 mg increase in dose 4.5; 95% CI [2.7, 7.3]; p <0.001), treatment with warfarin (OR 3.0; 95% CI [1.4, 6.2]; p = 0.003), comorbid disease (OR 2.1; 95% CI [1.3, 3.4]; p = 0.001), endoscopy performed in July or August (OR 2.0; 95% CI [1.1,3.7]; p = 0.02), and age (OR for each 1 year increase in age 1.03; 95% CI [1.01, 1.05]; p = 0.01) were identified at multiple logistic regression as independent predictors of negative outcomes.

Patients taking warfarin were significantly more likely to experience rectal bleeding than those not taking warfarin. No statistical differences were found in those patients using NSAIDs or taking aspirin with respect to adverse outcomes.

Bowles et al. 2004 (5) conducted a prospective survey on three National Heals service regions in the UK to assess quality of colonoscopies performed. They reported information on 9,223 colonoscopies, 234 colonoscopists, and 599 patients. Useful information are reported about caecal intubation rate and reason for incomplete colonoscopies: caecal intubation rate are lower in patients with ASA III, in females, in patients aged over 75, when sodium picosulphate (Picolax) is used. It is higher in private hospitals compared to teaching and District General Hospital. Reason for incomplete colonoscopy were reported as: patient discomfort (34.7%) looping (29.7%) poor bowel preparation (19.6%).

Bernstein et al. 2005 (6) identified patient, procedure, and endoscopist-related factors associated with caecal intubation time and factors that predict prolonged caecal intubation time (20 minutes or more) in a prospective study on 693 colonscopies. They performed a logistic regression analysis using the caecal intubation time as outcome measure. They found that the following factors were associated with longer caecal intubation time:

- older patient age,
- female gender,
- lower BMI,
- poor bowel preparation,
- fewer annual colonoscopies performed by the endoscopist

Lee et al, 2008 (7) assessed the factor associated with longer caecal intubation time. A total of 4,351 colonoscopies were assessed from 24 tertiary care centres in Korea. Multivariate analysis was used to evaluate the independent impact on the success of caecal intubation.
The authors found that prolonged caecal intubation was caused by the following factors:

- elderly patients
- female sex
- low body mass index
- poor bowel preparation
- poor American Society of Anesthesiologists status
- abdominal pain as an indication
- instructor's supervision
- low case volume

Authors concluded that Competence in technically efficient screening and diagnostic colonoscopy generally requires experience with more than 150 cases.

Harris et al, 2007 conducted a prospective observational study assessing the factors associated with technical performance (8). 6,004 patients were included in the study.The study focused on three specific quality indicators:
- Completion of colonoscopy
- Frequency of adenomatous polyps
- Procedure duration

Complete colonoscopy

Factors associated with the probability of having a complete colonoscopy include:

Positives factors:
- Health status, those in good health were more likely to have a complete colonoscopy than those in poor health
- Patients in private, open-access centres were more likely to have a complete colonoscopy than patients in public, open-access or gatekeeper centres.
- High quality of bowel preparation
- patients that had deep sedation were more likely to have a complete colonoscopy than those with no sedation

Negative factors:
- Gender, women were less likely to have a complete colonoscopy than men
- Having a colonoscopy in centre with annual volume less than 1500 examination per year
- having a colonoscopy in centres where over 50% of endoscopists were of senior rank is associated with less probability to have a complete colonoscopy
- use of fluoroscope
- Poor tolerance or pain
- diverticular disease
- prior abdominal surgery
- Frequency of adenomatous polyps
- Having colonoscopy in centres where over 50% of the endoscopists were of senior rank were roughly twice as likely to have an adenoma diagnosed.
- Longer average withdrawal duration was associated with more frequent adenoma diagnoses.
- High quality of colon cleansing
- Gender, women were less likely to have an adenoma diagnosed than men
- Procedure duration
- Having difficulty during colonoscopy is associated with longer duration to the cecum and longer withdrawal duration
- having a colonoscopy in a private centre vs public is associated with less duration
- having a colonoscopy where more than 50% of endoscopists were senior is associated with longer duration

Retrospective studies

Anderson et al, 2000 (9) assessed the clinical features and risk factors for colonic perforations in 10,486 colonoscopies. Female patients were 2.5 times more likely to have a colonic perforation than men. Trainee endoscopists were involved in 20% of the examinations and 40% of the perforations

occurred while the trainee fellow was involved in the case. The authors concluded that the following circumstances seem to represent situations with increased risk for colonoscopic perforation:

1) Unusual difficulty in traversing the sigmoid colon.
2) Any difficult examination in a female patient.
3) Moderate difficulty during any examination by a trainee endoscopist
Hui et al, 2004 (10) investigated adverse outcomes of colonoscopy and anticoagulants and antiplatelets by retrospectively reviewing colonoscopy cases. The risk of post-polypectomy bleeding was significantly higher among patients who received warfarin before colonoscopy (p <0.001). Age, the location and size of polyp, the use of aspirin, non-steroidal anti-inflammatory drugs, and other antiplatelet agents were not associated with a higher risk of polypectomy-associated bleeding.

Shah 2007 (11) performed a retrospective study on 331,608 Men and women 50 to 74 years of age who underwent a colonoscopy. The first (index) colonoscopy was classified as complete or incomplete. A generalized estimating equations model was used to evaluate the association between patient, endoscopist (specialty, colonoscopy volume), and setting (academic hospital, community hospital, private office) factors and incomplete colonoscopy. 13% 1 of colonoscopies were incomplete. The factors most strongly associated with incomplete colonoscopy were increased patient age, female sex, and having the procedure in a private office.

Narrative review
Garrett et al. 2007 (12) examined the risks of anticoagulation usage before endoscopic procedures. The review is of very poor methodological quality because it does not describe the included studies. Authors reported the recommendation of the ASGE guideline which state that:

Aspirin: in standard dosing has not been shown to increase the risk of postprocedural bleeding.

Antiplatelet agents: There are limited safety data for newer antiplatelet agents, including clopidogrel, and recommendations regarding their use before endoscopy have not been made.

Warfarin: the guidelines define procedures such as diagnostic EGD and colonoscopy as low risk, and can be undertaken without stopping anticoagulation. High-risk procedures such as colonoscopic polypectomy and ERCP with sphincterotomy should be performed after discontinuing warfarin for 3 to 5 days. The recommendation for IV heparin or low-molecular weight heparin during warfarin withdrawal depends on the risk of a thromboembolic event of each individual patient.

CONCLUSIONS

The purpose and methods described in the above studies are different and generally not comparable across studies. In addition, patient inclusion and exclusion criteria varied between the studies making comparisons difficult.

In summary, the papers reviewed suggest the following patient variables need to be identified / taken into account prior to FS or colonoscopy because they can be associated with more adverse events, more time duration, incomplete examination:
- Use of anticoagulants e.g. warfarin
- Female anatomy
- Age of patient
- ASA status
- Prior abdominal surgery
- BMI
- diverticular disease

The following variables related to poor performance of the examination can be associated with adverse effects, more time duration, incomplete colonoscopy

- Poor bowel preparation is associated with lower rate of complete colonoscopy
- Deep sedation is associated with higher rate of complete colonoscopy
- Having a colonoscopy in a private centre vs public is associated with less procedure duration and higher rate of complete colonoscopy
- Low case volume is associated with mixed results. In some studies, centres with low case volume have a higher rate of incomplete colonoscopy whereas in other studies the opposite association has been found

Level of experience of endoscopist – trainee/experience. Also this variable is associated with mixed results: one study concluded than at least 150 examinations should be completed to have the necessary expertise, another study found that fewer annual colonoscopies performed by the endoscopist is associated with longer caecal intubation time whereas other studies found that having a colonoscopy where more than 50% of endoscopists were senior is associated with longer duration and less probability to have a complete colonosocpy
LEVEL OF EVIDENCE: III,IV,V

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5.1.2 Evidence tables

Author, publication year	Study objective Study design	Study Participants	Outcomes	Results	Conclusions Level of evidence
Eloubeidi, et al. 2003.	The aim of this study was to determine factors associated with a shorter or limited screening FS. Cross-sectional study USA	A total of 3980 patients (52% female) were prospectively enrolled in a screening program over a 22-month period.	Depth of the examination Major complication Minor complication Factors predicting limitation of the FS	Females were almost twice as likely as males to have a procedure limited in some way (angulation, spasm, or pain) (OR _1.86, 95% CI _ 1.63–2.13). The average endoscopy distance for women was 52.3 cm, compared with 55.2 cm in men (p _ 0.0001). Average number of polyps detected in women was 1.4, compared with 1.56 in men (p _ 0.003) among patients with at least one polyp. Multivariate analysis Females were more likely to have an examination of <50 cm compared with men, controlling for age, spasm or pain on examination, previous surgery, angulation of the colon, and type of endoscopist—MD or nonphysician endoscopist (OR _ 1.67, 95% CI _ 1.41–1.99). Three factors predictive of a limited examination are similar to those that predict a depth of examination of _50 cm, including female gender (OR _ 1.83 95%CI1.60-2.10), age (OR _ 1.01 95%CI 1.02-1.03), and previous pelvic or abdominal surgery (OR _ 1.29 95%CI 1.12-1.49). The presence of diverticulosis is also related significantly to a limited examination (OR _ 1.79, 95% CI _ 1.47–2.20). Among patients only experiencing spasm/pain on examination, the independent predictors were female gender (OR _ 2.18, 95% CI _ 1.71–2.80), prior barium enema (OR _ 1.39, 95% CI _ 1.06 –1.82), and diverticulosis (OR _ 2.70, 95% CI _ 2.03–3.60). For patients with angulation, the only independent predictor in a multivariate analysis was female gender (OR _ 1.64, 95% CI _ 1.31–2.05)	**V** The results support an increased risk for a limited examination for females, patients with a history of pelvic or abdominal surgery, older patients, and patients with diverticulosison examination. Female gender was a significant factor associated with a limited screening FS. Women were more likely to experience pain or spasm and to have colonic angulation and were less likely to have their sigmoid colon adequately visualized. This is in part explained by a prior history of abdominal or pelvic surgery. This is partly owing to increased colonic angulation and pain during the examination. Methods aimed at reducing pain and improving maneuverability in an angulated colon during FS may improve the effectiveness of CRC screening in women.

Quality assessment: Study sample is truly representative of people at average risk of colorectal cancer in the community. Men and women were selected from the records of an individual medical practice – Harvard Vanguard Medical Associates, Boston, MA. Eligibility criteria for the study described. Results presented descriptively and in tabular format. Statistical analyses of outcomes described. Patients were not followed up in this study and there was no exit questionnaire.

Author, publication year	Study Objective Study design	participants	outcomes	Results	Level of evidence Conclusions
Viiala 2008	To assess the outcomes for women in a flexible sigmoidoscopy based screening program. Cross-sectional study Australia	3,402 participants (women 41%). at the programme of unsedated FS-based screening of asymptomatic average-risk individuals aged 55–64 years	Insertion depth Pain score in men and women	Mean age of participants = 59.6 years. Median insertion depth: Men: 60 cm (range 15–120 cm) Women:50 cm (range 4–100 cm) (P <0.0001 Women were more likely to undergo a FS with insertion depth less than 40 cm (17% vs 6%, P <0.0001). Mean pain score was 2.9 for men and 4.0 for women (P <0.0001).	**V** This study of screening FS has shown that compared to men, women will probably find the procedure more uncomfortable and have a lower insertion depth. Previous hysterectomy appears to be a significant factor although there also appear to be inherent anatomical variations between the colons of women and men.

Quality assessment: The study sample is truly representative of people at average risk of colorectal cancer in the community (Fremantle Hospital in Western Australia has been conducting a community-based screening programme for colorectal neoplasia using FS since 1995. Since inception, more than 3400 screenings of average-risk individuals have been carried out).The authors commented on the limitations of this study, comments include the reliance on insertion depths and biopsy distances reported by numerous different proceduralists and there may have been variations in practice and technique between them. No standardized technique for deciding the point of maximal insertion was used. Insertion depth has been shown to be an unreliable marker of anatomical extent of examination.

Author, publication year	Objective Study Design	Participants	Outcomes	Follow-up	Results	Level of evidence Conclusions
Rathgaber 2006	To collect and report the completion and complication rates of colonoscopy in a community gastroenterology practice. Single-center cohort study: completion rate assessed prospectively; complication assessed retrospectively every month reviewing all hospitalisation Setting: Community gastroenterology practice. USA	A total of 12,407 consecutive patients referred for colonoscopy; mean age, 59.7 years; 5925 men.	Completion of colonoscopy to cecum or ileocolonic anastomosis. Complications of haemorrage and perforation Reason for not completing colonoscopy	1 month	A colonoscopy was completed in 98.4% of patients. Completion of colonoscopy: Men:98.8% Women:98.0% P:<0.001 Polypectomy was accomplished in 5074 (40.9%). Causes for failure included: difficult anatomy (55.9%),men:o.56%, women: 1.19% P:<0.001 inadequate preparation (20.8%); men: 0.30%, women: 0.35% P:ns obstructing malignancy (8.6%), men: 0.14%, womwn:0.14%, P:ns discomfort (8.1%), men: 0.07%, women: 0.14% P:ns, severe inflammation (6.1%). Men: 0.10, women: 0.09 P:ns Complications: Haemorrhage requiring hospitalisation occurred after 25 cases (0.20%). Twenty-three episodes of bleeding occurred after polypectomy (0.46%) and 2 after treatment of arteriovenous malformations. Two perforations occurred (0.016%). One patient developed a posterior circulation stroke. No differences between male and female were noted	III Sex differences in failure to complete colonoscopy have been reported previously.. Our overall completion differences between sexes were not large, but failure because of anatomic causes was significantly more common in women. A trend for more failure from pain/discomfort in women represented in this study could be related to similar anatomic issues or more irritable bowel syndrome and visceral hypersensitivity in female populations.

Quality assessment: Inadequate description of the cohort, likely to be somewhat representative of average risk of CRC in the population. Ascertainment of exposure by clinical records. Biases relating to patient selection not discussed. No mention of adjustments e.g. age. Assessment of outcomes by record linkage No statement about completeness of follow up.

The authors reported the following weaknesses in the study; primarily they rest on the reporting mechanisms. The validity relies upon accurate reporting of completion upon recognition of landmarks. This possibility of bias is inherent in these types of studies, because it is impractical to have a second confirmatory colleague present for the procedure. Still photography is not perfect at allowing later confirmation of caecal intubation. Although photography was frequently used during our procedures, this was not a requirement, because photo documentation is a poor criterion standard. At best, there is an 80% to 85% inter-observer agreement. At worst, it is less than 50%. Therefore, every study that reports caecal intubation faces this limitation. As a result our completion rate may be overstated.

Author, publication year	Study objective Study design	Study Participants	Outcomes	Follow up	Results	Conclusions Level of evidence
Bini et al. 2003	The primary aim of this study was to prospectively determine the frequency of negative outcomes within 30 days of outpatient EGD, colonoscopy, and flexible sigmoidoscopy in a training program setting. Secondary aims were to evaluate risk factors for negative outcomes and to assess whether these were associated with decreased patient satisfaction. Prospective cohort study. Questionnaires were mailed to 1000 consecutive patients 30 days after endoscopy to evaluate procedure-related negative outcomes (serious and minor adverse events) and patient satisfaction. USA	1,000 consecutive patients undergoing outpatient EGD, colonoscopy, combined EGD and colonoscopy, or flexible sigmoidoscopy at a Veterans Affairs hospital were enrolled in the study.	Serous adverse events Minor adverse events Risk factor associated with adverse events	1 month	30-day frequency of negative outcomes in 869 (87%) patients who responded was 14.3%. • 0.6% were serious • 13.7% were minor adverse events. Frequency of negative outcomes : 17.1% for EGD, 15.0% for colonoscopy, 24.4% for combined EGD and colonoscopy 7.8% for flexible sigmoidoscopy. Multiple logistic regression identified midazolam dose (OR for each 1 mg increase in dose 4.5; 95% CI [2.7, 7.3]; p <0.001), treatment with warfarin (OR 3.0; 95% CI [1.4, 6.2]; p = 0.003), comorbid disease (OR 2.1; 95% CI [1.3, 3.4]; p = 0.001), endoscopy performed in July or August (OR 2.0; 95% CI [1.1,3.7]; p = 0.02), and age (OR for each 1 year increase in age 1.03; 95% CI [1.01, 1.05]; p = 0.01) as independent predictors of negative outcomes. There was a significant association between negative outcomes and decreased patient satisfaction, and patients who reported negative outcomes were less likely to agree to endoscopy in the future.	III Serious adverse events were rare after endoscopy performed by gastroenterology fellows. Contacting patients 30 days after outpatient endoscopy significantly improved the detection of negative outcomes. Although the majority of negative outcomes were minor, these adverse events were associated with decreased patient satisfaction.

Quality assessment: Representativeness of the exposed cohort: selected group of patients not truly representative: the study was conducted at a single centre and the results may not be generalisable. Second, the study evaluated negative outcomes after endoscopy performed by a small number of gastroenterology fellows at different levels of training. This may result in an operator-dependent variable that influences the adverse event rates, and a multicenter study with a large number of fellows is necessary to further evaluate negative outcomes after endoscopy in the training setting. Third, the majority of our patients were elderly men (mean age 68.6 years).

Ascertainment of exposure by clinical record.

Most important factor of adjustment accounted for.

Assessment of outcomes by self report: questioning patients about negative outcomes and satisfaction 30 days after the procedure may be subject to recall and response bias. Patients may forget to report adverse events that occur immediately after the procedure. However, patients are unlikely to forget serious adverse events such as postpolypectomy bleeding or colonic perforation. Fifth, the definition of negative outcomes used in the present study may differ from that used in other studies. The survey questionnaire used in the current study did not specify the timing of the negative outcome in relation to the procedure and cannot prove causality. Although patients were specifically asked about adverse events they felt were related to endoscopy, a control group of patients who did not undergo endoscopy was not included. Therefore, the study may have overestimated the frequency of negative outcomes because patients may have reported symptoms that were unrelated to the endoscopic procedure

Subject lost at follow up 13%. Authors reported that there were no significant differences between the 869 patients contacted and the 131 individuals who could not be contacted by mail or telephone (data not shown).

Author, publication year	Study objective Study design	Participants	Outcomes	Results	Level of evidence Conclusions
Anderson 2000	To assess the incidence, clinical features, and management of endoscopic colon perforations in a large number of patients at a major medical teaching center. A retrospective review of medical records of all patients with colon perforations from endoscopy over a 10-yr period USA	10,486 Patients admitted at the Mayo Clinic for colon perforation	Frequency of perforation after colonoscopy Risk factor for perforation	perforation after colonoscopy: 20 (0.19%) Twelve perforations occurred after a diagnostic colonoscopy, and eight perforations occurred after therapeutic colonoscopy The majority of perforations (65%) occurred in the sigmoid colon. Multivariate analysis using gender and age showed that female gender was an independent predictor of a higher risk of perforation (p , 0.05). Trainees Trainee endoscopists were involved in only 20% of the colonoscopies performed, 8 (40%) perforations occurred while the training fellow was involved in the case. However, this increased risk of perforation with a training fellow was not statistically significant (p 5 0.625). Females were two and a half times more likely to have a colonic perforation compared with men; however, this did not reach statistical significance.	IV Colonoscopy can result in significant morbidity and carries a small risk of death. Sigmoidoscopy has lower risk. The following situations may represent increased risk to colonoscopy patients: unusual difficulty in traversing the sigmoid colon; difficult examinations in female patients, and difficult examinations performed by trainee physicians.

Quality assessment: Selection of patient records from hospital database described (dates provided). Assessment of exposure and outcomes by clinical records. Some important factor for counfounding adjusted for. Exclusion criteria specified. Patient follow-up described.

Author, publication year	Study objective Study design	Participants	outcomes	Results	Conclusions Level of evidence
Hui et al. 2004.	The aim of this study was to review patients that had undergone colonoscopic polypectomy to investigate the risk of bleeding with anticoagulants and antiplatelet agents. A retrospective audit was conducted of patients undergoing colonoscopy at a tertiary referral endoscopy center Patients with post-polypectomy bleeding are compared to those without.	5,593 cases were reviewed. Polypectomy was performed in 1657 patients.	Immediate and delayed (in one month) bleeding. risk factors for bleeding :age; size of polyp; location of polyps (colon divided into cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum); method of polypectomy (snare or "hot biopsy"); use of antiplatelet agents (aspirin, ticlopidine, clopidogrel), NSAIDs, or warfarin; skill of the endoscopist (trainee or instructor); and presence of underlying renal impairment.	.Bleeding group = 37 (2.2%) Non-bleeding group = 1620. bleeding was immediate in 32 and delayed in 5. Multivariate analysis showed that warfarin use, after adjustment for the effects of each of the other factors, was an independent risk factor for bleeding, with an odds ratio 13.37: 95% CI[4.10, 43.65]. Age; the location and size of polyp; and the use of aspirin, non-steroidal anti-inflammatory drugs, and other antiplatelet agents were not associated with a higher risk of polypectomy-associated bleeding.	**IV** The main finding of the present study was that the use of antiplatelet agents and NSAIDs alike is not associated with an increased frequency of postcolonoscopic polypectomy bleeding. In contrast to antiplatelet agents, the results of the present study show that anticoagulants, such as warfarin, increases the risk of post-polypectomy bleeding and should be stopped and the INR normalized before performing an elective colonoscopy in which therapeutic maneuvers are anticipated.

Quality assessment: Definition of cases and controls by record linkage. Ascertainment of exposure by structured interview. Same method of assessment for cases and controls. Most important factor for adjustment accounted for.This retrospective study has limitations. First, preparation of patients for colonoscopy and the identification and management of post-polypectomy bleeding were not standardised. Second, there was no structured follow-up for patients after colonoscopy. Thus, patients who presented to a private clinic or hospital with post-polypectomy bleeding would have been missed. However, data collection was reasonably complete, with the help of the on-line patient database for the Hospital Authority of Hong Kong. This system covers 44 general hospitals in the territory of Hong Kong and contains detailed inpatient and out-patient records, including procedure records, e.g. for endoscopies.

Author, publication year	Study Objective	Study design	Results	Level of evidence Conclusions
Garrett et al. 2007	To review the current data and societal guidelines assessing risks of anticoagulation, including antiplatelet agents, before endoscopic procedures.	Narrative Review. The MEDLINE database was searched for pertinent randomised control trials, systematic reviews, observations studies, and current practice guidelines from major societies. Additional studies were identified from the reference lists of reviewed articles.	Number of studies retrieved and included in the review not stated The rate of postprocedure bleeding, with or without anticoagulation, is low. Most data were from small case series studying bleeding after colonoscopic polypectomy. Societal guidelines addressed postprocedure bleeding more broadly. The most complete guidelines are from the American Society for Gastrointestinal Endoscopy. Aspirin: in standard dosing, aspirin has not been shown to increase the risk of postprocedural bleeding. Antiplatelet agents: There are limited safety data for newer antiplatelet agents, including clopidogrel, and recommendations regarding their use before endoscopy have not been made. Warfarin: the guidelines define procedures such as diagnostic EGD and colonoscopy as low risk, and can be undertaken without stopping anticoagulation. High-risk procedures such as colonoscopic polypectomy and ERCP with sphincterotomy should be performed after discontinuing warfarin for 3 to 5 days. The recommendation for IV heparin or low-molecular weight heparin during warfarin withdrawal depends on the risk of a thromboembolic event of each individual patient.	Not assessable because the designs of included studies are not reported Management of anticoagulation and antiplatelet therapy before endoscopy depends on the patient's risk of thromboembolism balanced with the bleeding risk of the procedure. Decisions should be individualized with consideration of the underlying medical condition requiring anticoagulation, the patient's overall health status, and the procedure to be performed.

Quality assessment: Narrative review. Bibliographic search not specified in detail. Inclusion and exclusion criteria for primary studies not defined, number of included studies not stated. Results of primary studies presented narratively. ASQE guidelines presented in a table.

Author, publication year	Study objective Study Design	Study Participants	Outcomes	Results	Conclusions Level of evidence
Bowles et al. 2004	To study the availability and quality of adult and paediatric colonoscopy in three National Health Service (NHS) regions. Cross-sectionnal survey UK	Sixty eight units provided information on 9223 colonoscopies, 234 colonoscopists, and 599 patients.	caecal intubation rate Reason for incomplete colonoscopy	Caecal Intubation rate for type of hospital District General Hospitals:74.5% teaching hospitals 76.6% private hospitals 89.7% paediatric hospitals 73.8% Caecal intubation rate for ASA status ASA status 1: 80.4% ASA status 2: 73.5% ASA status 3: 66.3% ASA status 4: 64.9% Caecal intubation by age 16 years: 77.5% 17–75 years: 78.1% >75 years: 70.7 Caecal intubation rate by sex Males: 80.5% females:73.4% Caecal intubation rate for single agent bowel preparation sodium phosphate (Fleet) 82.1% sodium picosulphate (Picolax) 72.8% polyethylene glycol preparations (Klean prep) 80.9% The caecal intubation rate was similar whether or not hyoscine butylbromide was given (80.4% versus 76.9%). Reasons for failing to reach the caecum • patient discomfort (34.7%) • looping (29.7%) • poor bowel preparation (19.6%).	V

Author, publication year	Study objective Study Design	Study participants	outcomes	Results	Conclusion Level of evidence

Bernstein et al. 2005	To identify patient, procedure, and endoscopist-related factors associated with caecal intubation time. to identify factors that predict prolonged caecal intubation time (20 minutes or more)
	
	prospective observational study
		A total of 693 consecutive outpatient colonoscopies performed. USA	<u>Patient related factors:</u> age, gender, BMI, and surgical history, presence of diverticular disease
			<u>Procedure related factors</u>: quality of bowel preparation
			<u>Endoscopist related factors</u> : experience (number of colonoscopies performed during the previous year) and fellow
			A linear regression model was developed by using the log of caecal intubation time as the outcome variable
				Complete data were available for 587 patients.
				Logistic regression model demonstrates that the following factors were associated with longer caecal intubation time:
				  older patient age,
				  female gender,
				  lower BMI,
				poor bowel preparation,
				fewer annual colonoscopies performed by the endoscopist.
					III
					
					In summary, this large prospective study demonstrated that colonoscope insertion time is prolonged by the following factors: older age, lower BMI, poor quality of bowel preparation, female gender, and fewer colonoscopies performed by the endoscopist in the previous year. Factors associated with prolonged caecal intubation time (20 minutes or more) are lower BMI, poor quality of bowel preparation, and fellow involvement in the procedure.

Quality assessment: cohort is representative of people at average risk of colorectal cancer in the community. Ascertainment of exposure by clinical records. Most important confounding factor adjusted for; subjects lost to follow up >5% reason given

Author, publication year	Study Objective Study Design	Study Participants	Outcomes	Results	Conclusions Level of evidence
Lee et al. 2008	The purpose of this study was to determine the adequate level of training for technical competence in screening and diagnostic colonoscopy. An observational prospective multicentre study Multivariate analysis was used to evaluate the independent impact on the success of caecal intubation.	Over 8 months the authors prospectively evaluated the procedures of 24 first-year GI fellows in 15 tertiary care academic medical centers. A total of 4351 colonoscopies were assessed. Patient exclusion criteria were (1) emergency colonoscopy, (2) colon obstruction, (3) history of colon operations, (4) therapeutic procedure (including polypectomy), (5) surveillance of inflammatory bowel disease, and (6) people over 80 years of age or under 18 years of age. Korea	Caecal intubation time Factor affecting caecal intubation time	The overall success rate in reaching the cecum in 20 minutes was 83.5% (3635/4351). <u>Caecal intubation time</u> Mean over the 8 months = 9.23 ± 4.63 minutes. Decreased significantly, from 11.16 to 8.39 minutes, after 150 procedures and continuously improved afterward. <u>Trainee learning curve for caecal intubation</u> The success rate significantly improved and reached the requisite standard of competence after 150 procedures (71.5%, 82.6%, 91.3%, 94.4%, 98.4%, and 98.7%, respectively, for every 50 consecutive blocks). Multivariate logistic regression analysis was performed with the outcome variable being caecal intubation time of less than 20 minutes versus 20 minutes or more. The following factors were associated with prolonged caecal intubation (O20 minutes): elderly patients: OR 1.01 (CI95% 1.00-1.02) female sex: OR 1.35 (CI95% 1.11-1.62) low BMI: OR: 0.96 (CI95% 0.93-0.99) poor bowel preparation: OR 1.04 (CI95%1.00-1.08) poor American Society of Anesthesiologists (ASA) status: OR: 2.0 (CI95% 1.53-2.62) abdominal pain: OR 1.28 (CI95% 1.00-1.64) influence of instructor's supervision OR:2.54 (CI95% 2.06-3.12) <u>Polyp detection rate (>5mm)</u> • All colonoscopies: 21.8% • Male vs. female: 26.5% vs. 14.9% • Trainees: polyp detection did not improve significantly during the 8 months and was not correlated with the learning curve. •	**III** Competence in technically efficient screening and diagnostic colonoscopy generally requires experience with more than 150 cases. Also, factors associated with prolonged caecal intubation for typical trainees did not differ from those for experienced colonoscopists. Prolonged caecal intubation was caused by the following factors: • elderly patients • female sex • low body mass index • poor bowel preparation • poor American Society of Anesthesiologists status • abdominal pain as an indication • instructor's supervision • low case volume.

Quality assessment: Cohort was drawn from multiple centres. Exclusion criteria defined. Outcome measures defined. Follow up not described. The main limitation of our study is the method of evaluating the polyp detection rate. We had limited power because final pathologic report and withdrawal time were not included.

Author, publication, year	Study Objective Study Design	Study Participants	Outcomes	Results	Conclusion Level of evidence
Harris et al. 2007	To determine factors associated with three performance indicators in endoscopy centres internationally: -Completion of colonoscopy - Frequency of adenomatous polyps - Procedure duration Observational prospective study multiple variable regression analyses to identify determinants of the quality indicators.	Consecutive patients referred for colonoscopy from 21 centres in 10 European countries (Czech Republic, Denmark, France, Germany, Great Britain, Italy, Poland, Spain, Sweden, Switzerland) and Canada..	Factors which can affect: - Completion of colonoscopy - Frequency of adenomatous polyps - Procedure duration	6004 patients included in the study. Factors associated with completed colonoscopy : - Having colonoscopy in a private, open-access centres were more likely to have a complete colonoscopy than in public, gatekeeper centres.(OR: 3.17, 95% CI: 1.87–5.38) - having a colonoscopy in centres where over 50% of endoscopists were of senior rank were less likely to have a complete colonoscopy (OR: 0.50- 95%CI 0.35-0.72) - having a colonoscopy in centres with an annual volume of more than 1500 colonoscopies were less likely to have a complete colonoscopy (OR: 0-54 95%CI 0.41-0.72) - high quality bowel preparation : high quality = 91.3% complete vs. low quality = 71.7% - Gender, women were less likely to have a complete colonoscopy than men (OR 0.74 95%CI 0.59- 0.92) - Health status, those in poor health were less likely to have a complete colonoscopy than those in good health (OR: 0.84 95%CI 0.64-1.10) - high quality of colon cleansing: OR: 3.71 (95%CI 2.83, 4.87) - deep sedation vs none: OR 2.69 (95%CI 1.78, 4.06) - use of fluoroscope: OR: 0.60 (95%CI 0.42, 0.85) - Poor tolerance or pain: OR: 0.21 (95%CI 0.16, 0.27) - diverticular disease: OR: 0.46 (95%CI 0.32, 0.67) - prior abdominal surgery: OR: 0.38 (95%CI 0.28, 0.52) Factors associated with frequency of adenomatous polyps - Having colonoscopy in centres where over 50% of the endoscopists were of senior rank were roughly twice as likely to have an adenoma diagnosed. - Gender, women were less likely to have a adenoma diagnosed than men (OR 0.57 95%CI 0.47- 0.68) - Longer average withdrawal duration was associated with more frequent adenoma diagnoses. (OR: 1.08, 95% CI: 1.07–1.09) - High quality of colon cleansing OR: 1.69 (95%CI 1.12-2.64)	III Multiple factors have been identified as being associated with key quality indicators. The non-modifiable factors (type and size of centre, age, gender) permit the identification of patients who may be at greater risk of not having quality colonoscopy, while changes to the modifiable factors (sedation, cleansing) may help improve the quality of colonoscopy.

Author, publication, year	Study Objective Study Design	Study Participants	Outcomes	Results	Conclusion Level of evidence
				Factors associate with procedure duration - having a colonoscopy in a private centre vs public: OR: 0.62 (95%CI 0.58, 0.66) - having a colonoscopy where more than 50% of endoscopist were senior OR: 1.13, 1.24 <0.001 - Having difficulty during colonoscopy had longer durations to caecum (time ratio: 2.87, 95% CI: 2.72–3.01) and withdrawal durations (time ratio: 1.26, 95% CI: 1.18–1.33) than patients who had no difficulties.	

Quality assessment: Cohort drawn from multiple centres in Europe – 21. Internationally derived patient cohort. Outcomes described. There are a few limitations to this study that should be noted. First, several variables used in this study were based at the centre level when these would have been more accurately determined at the patient level, for instance seniority of the endoscopist and waiting time for colonoscopy. Secondly, even though all patients who underwent colonoscopy were to be consecutively included in the study and data completeness was required of all participating centres, it is possible that not all colonoscopy patients were, in fact, included. However, the inclusion period of each centre corresponded with their stated annual volume of colonoscopies, indicating that most, if not all, patients who underwent colonoscopy were indeed included in the study. Lastly, although this study of 21 centres from 11 countries provided a wide range of patients from a wide range of settings, the sample of centres was a convenience sample and may therefore not be representative of all endoscopy centres and all patients undergoing colonoscopy, and thus, may not be generalisable to other endoscopy centres.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Shah 2007	To determine the colonoscopy completion rate and to identify factors associated with incomplete procedures Cross-sectionnal study	331,608 Men and women 50 to 74 years of age who underwent a colonoscopy. USA	Colonoscopy	The first (index) colonoscopy was classified as complete or incomplete. A generalized estimating equations model was used to evaluate the association between patient, endoscopist (specialty, colonoscopy volume), and setting (academic hospital, community hospital, private office) factors and incomplete colonoscopy.	Incomplete colonoscopy: 13.1% Patients with an incomplete colonoscopy were older (odds ratio [OR] 1.20 per 10-year increment; 95% CI] 1.18–1.22), more likely to be female (OR 1.35; 95% CI: 1.30–1.39), have a history of prior abdominal surgery (OR 1.07; 95% CI: 1.05–1.09) or prior pelvic surgery (OR 1.04; 95% CI: 1.01–1.06). For colonoscopies done in a private office, the odds of an incomplete procedure were more than 3-fold greater than for procedures done in an academic hospital (OR 3.57; 95% CI: 2.55–4.98)	V The factors most strongly associated with incomplete colonoscopy were increased patient age, female sex, and having the procedure in a private office.

5.2   Bowel preparation

5.2.1   Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 4

What regimens and schedules provide an optimal bowel preparation for FS and colonoscopy, with minimal side effects and patient discomfort?

PICOS

P: General population at average risk of CRC (age 50 or older) and individuals with a positive FOBT/FIT
I: Regimens and schedules for FS and colonoscopy
C: Different regimens
O: Bleeding, perforation, infections, pain/discomfort, completeness
S: RCTs, systematic and narrative reviews, cohort and case control studies.

<u>COLONOSCOPY</u>

SEARCH METHOD

In the first instance systematic reviews of randomised controlled studies were searched. Search was performed in August 2008 and limited to reviews published between 2000 and 2008.
Search strategy: <u>MedLine</u>: 'optimal bowel preparation and colonoscopy AND systematic review'.

RESULTS

One systematic review was retrieved for this question.

Belsey et al, 2007 (1) reviewed RCTs comparing two or more bowel preparation regimens in terms of efficacy and tolerability. The review was of good methodological quality. 82 RCts were included. The comparisons found were the following: PEG vs. sodium phosphate (25 studies), different PEG formulations and dose regimens (33 studies) , different Sodium phosphate formulations and dose regimens (7 studies), Miscellaneous regimens (28 studies). Meta-analysis was possible only for adequacy of preparation in studies comparing PEG vs Sodium Phosphate and resulted in no significant difference between preparations (OR: 0.94 [95%CI 0.64, 1.39]).

This systematic review found that no single bowel preparation emerged as consistently superior.
The authors concluded that the efficacy of current bowel preparations was not significantly different, but sodium phosphate was better tolerated. The authors identified a need for rigorous study design that will enable unequivocal conclusions to be drawn on the safety and efficacy of bowel preparations.

CONCLUSIONS

To date, no single bowel preparation emerged as consistently superior over another. Authors underline that the relatively small size of many trials, inconsistent outcome assessment and design weakness make it difficult to draw clear conclusions. Moreover interpretation of the studies is limited by the inconsistent and poorly defined measures of efficacy outcome (LEVEL OF EVIDENCE I).

REFERENCES

1. Belsey J, Epstein O & Heresbach D (2007), Systematic review: oral bowel preparation for colonoscopy, *Aliment.Pharmacol.Ther.*, vol. 25, no. 4, pp. 373-384.

SIGMOIDOSCOPY (FS)

SEARCH METHOD

Searches were conducted on <u>MedLine</u> for RCTs, systematic reviews, meta-analyses and clinical trial published in English between 2000 and January 2009.
<u>MedLine</u>
The following free text searches produced 28 results with 6 papers (1 review, 4 RCTs and 1 trial) deemed relevant:
 (FS AND preparation) OR (sigmoidoscopy AND preparation) OR (FS AND bowel preparation) OR (sigmoidoscopy AND bowel preparation)

The review found (Brown, 2004 (1)) was not considered and was replaced by the related references (Bini, 2000 (2) and Fincher, 1999 (3)) because the review did not include specified result or result separated for gastrointestinal procedures.

RESULTS

Five randomised controlled trials were retrieved

RCTs

Fincher, 1999 (3) performed a randomised trial to compare three sigmoidoscopy preparations containing magnesium citrate (combining with oral bisacodyl, one hypertonic phosphate enema or two hypertonic phosphate enemas) in 291 outpatients undergoing flexible sigmoidoscopy.

Preparation quality was rated as excellent or good for 80.6% in the bisacodyl group, 88.7% in the one-enema group, and 85.1% in the two-enema group (p=0.30). Patients reported the oral bisacodyl regimen was better tolerated (p=0.032). Although the three regimens were comparable in most side effects, the bisacodyl preparation was associated with more diarrhea (p=0.0003). Mean procedure duration, mean insertion depth, and prevalence of diverticula and polyps were similar in all groups. Fewer than 4% of patients required repeat procedures due to poor preparation quality.

Bini, 2000 (2) conduced a randomised trial to compare patient tolerance, quality of preparation, and cost of 2 bowel cleansing regimens (oral or enema preparation) in 250 patients undergoing screening flexible sigmoidoscopy. Oral preparation consisted of oral bisacodyl followed by 45 mL oral sodium phosphate; enema preparation consisted of oral bisacodyl followed by 2 Fleet enemas. Patients in the oral preparation group were more likely to grade the preparation as easy or tolerable when compared with the enema group (96.8% vs. 56.4%, p <0.001). The endoscopist graded the quality of the preparation as good or excellent in 86.5% of the patients in the oral preparation group compared with 57.3% in the enema group (p <0.001). In the oral preparation group, the mean nursing time (34.6 vs. 65.3 minutes, p <0.001) and cost ($16.39 vs. $31.13, p <0.001) were significantly less than in the enema group.

Atkin, 2000 (4) evaluated with a randomised trial the acceptability and efficacy of two methods of self administered bowel preparation (a single phosphate enema and a single sachet of oral sodium picosulphate with magnesium citrate (Picolax) in 1442 patients undergoing screening flexible sigmoidoscopy). Compliance with the enema was higher than with the oral Picolax (608 (84%) v 566 (79%); difference 6%, 95% confidence interval 2% to 10%). Almost half of those who refused oral Picolax used an enema at home. Wind, incontinence, and sleep disturbance were more frequent in the Picolax group than the enema group; bottom soreness was more frequent in the enema group. Around 30% (187) found the diet restriction required by Picolax difficult; 78% (471) found the enema easy to administer. The quality of preparation was better with the enema; the proportion of procedures complete to the descending colon was greater and the mean duration of the procedure was shorter. There was no significant difference in polyp detection rates.

Gidwani, 2007 (5) assessed two methods of bowel preparation (two fleet enemas or lactulose and fleet enema) with the current standard (a single fleet enema) in an attempt to improve efficacy and acceptability in 261 outpatients undergoing flexible sigmoidoscopy.

No difference was noted between the groups with regard to patient acceptability variables (ease of use: $p = 0.09$; assistance required: $p = 0.11$; cramps experienced: $p = 0.84$; alternative method: $p = 0.25$). There was no significant difference between the groups in terms of depth of insertion ($p = 0.42$) or abnormalities noted ($p = 0.34$). Nor was there any difference in the quality of preparation of patients in group 1 versus group 2 ($p = 0.39$) or group 1 versus group 3 ($p = 0.13$). Authors concluded that the addition of a Fleet enema or oral lactulose over and above a single Fleet enema gives no significant improvement in the acceptability or efficacy of bowel preparation.

A single phosphate enema 2 h pre procedure is an effective method of bowel preparation for flexible sigmoidoscopy.

Ruangsin, 2007 (6) conduced a double blind randomised controlled trial comparing bowel preparation quality and patient tolerance of two common enema solutions in 300 patients undergoing flexible sigmoidoscopy. There were no serious complications during or following the procedures. The preparation quality was rated as excellent or good by 76.9% of the hypertonic sodium chloride group and 72.9% of the hypertonic sodium phosphate group ($p = 0.423$). The hypertonic sodium chloride enema was associated with more abdominal discomfort ($p = 0.018$). Both enemas were safe for all patients. Both preparations performed their bowel-cleaning function well and were suitable for the preparation of patients before flexible sigmoidoscopy

CONCLUSIONS

No significant difference in quality was found between oral preparation (Bysacodil or Picolax), one hypertonic phosphate enema or two hypertonic phosphate enemas, when considering quality of the preparation, proportion of complete exams and polyp detection rates. The largest trial showed a better performance of the enema group compared to the oral preparation, a smaller trial sowed a better performance of the oral preparation and the third trial showed equivalence of the different regimens.

The hypertonic sodium chloride enema and the hypertonic sodium phosphate enema are comparable for safety, acceptability and quality of bowel preparation.

No significant improvement was found in the acceptability or efficacy with the addiction of a second fleet enema or oral lactulose over a single fleet enema

Oral preparation was preferred over enema in one trial (using Bysacodil), but it was associated with a lower compliance in another study (using Picolax). Frequency of reported side effects was comparable both with enema and oral preparation, although different types of effects have been reported.
 (LEVEL OF EVIDENCE II).

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2. Bini EJ, Unger JS, Rieber JM, Rosenberg J, Trujillo K & Weinshel EH (2000), Prospective, randomised, single-blind comparison of two preparations for screening flexible sigmoidoscopy, *Gastrointest.Endosc.*, vol. 52, no. 2, pp. 218-222.

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4. Atkin WS, Hart A, Edwards R, Cook CF, Wardle J, McIntyre P, Aubrey R, Baron C, Sutton S, Cuzick J, Senapati A & Northover JM (2000), Single blind, randomised trial of efficacy and acceptability of oral picolax versus self administered phosphate enema in bowel preparation for flexible sigmoidoscopy screening, *BMJ*, vol. 320, no. 7248, pp. 1504-1508.

5. Gidwani AL, Makar R, Garrett D & Gilliland R (2007), A prospective randomised single-blind comparison of three methods of bowel preparation for outpatient flexible sigmoidoscopy, *Surg.Endosc.*, vol. 21, no. 6, pp. 945-949.

6. Ruangsin S & Chowchuvech V (2007), A randomised double-blind controlled trial comparing two forms of enema for flexible sigmoidoscopy, *J Med.Assoc.Thai.*, vol. 90, no. 11, pp. 2296-2300.

5.2.2 Evidence tables

Author, publication year	Study Objective Study design	Included studies	Results	Level of evidence Conclusions
Belsey et al. 2007	To identify high quality controlled trials comparing two or more bowel preparation regimens and to compare efficacy and tolerability. Systematic review **Quality assessment** of included studies performed; criteria reported	The search strategy identified 112 studies, 82 of which were included in the final analysis Comparisons: PEG vs. sodium phosphate n: 25 PEG formulations and dose regimens: n:33 Sodium phosphate formulations and dose regimens n: 7 Miscellaneous regimens n: 28	<ins>PEG vs. sodium phosphate</ins> Adequacy of preparation: OR 0.94 [95%CI 0.64, 1.39] Tolerability: meta-analysis not possible. Sodium phosphate was reported to be superior in 14, there was no significant difference in 10 and in only one was PEG considered the better tolerated preparation. <ins>PEG vs PEG</ins> splitting the dose into two equal segments, separated by 12 h, resulted in improvements in both bowel cleansing and patient acceptability. The closer the final dose is taken to the time of colonoscopy, the more effective the final cleansing. Concomitant use of metoclopramide, bisacodyl, cisapride, senna or magnesium citrate with PEG did not offer additional benefit, either in terms of efficacy of bowel cleansing, patient tolerability, or objective adverse events. Two small studies reported that low-volume PEG (1.5–2 L) yield similar bowel cleansing efficacy as that achieved with the standard regimen (3–4 L). One of these studies demonstrated improved tolerability. Most studies using this strategy have evaluated the use of low-volume PEG in combination with a prokinetic agent (bisacodyl, senna or magnesium citrate). In two of these combination studies, the high-volume regimen had superior efficacy, in three studies there was no significant difference, whilst in one study, the low-volume regime was found to be superior.63 In all five studies that investigated tolerability, low volume regime was preferred by patients. <ins>Sodium phosphate vs. sodium phosphate</ins> The seven NaP studies were designed as dose-finding comparisons, evaluating doses ranging from 45 to 180 mL of solution and 28 to 40 tablets. These studies demonstrated a clear dose–response both in terms of efficacy and tolerability, with the principle adverse events including nausea, vomiting and asymptomatic hyperphosphataemia. Dividing the doses reduced the incidence of nausea without sacrificing efficacy. Adverse events were reduced with the tablet formulation, although the large number of tablets required reduced patient acceptability and bowel cleaning efficacy was not as effective as the solution.	**I** Shortcomings in study design limit the value of many of the studies. Based on these results, no single bowel preparation emerges as consistently superior. New preparations are required that combine better efficacy and tolerability, in addition to rigorous new validated study designs, allowing unequivocal comparisons to be made. The optimum combination of efficacy, tolerability and safety has yet to be defined for bowel preparation for colonoscopy. There is clearly a need for new preparations and an imperative to develop new and validated methods of assessing efficacy and tolerability using rigorous study designs that will allow unequivocal conclusions to be drawn from adequately powered controlled trials

Author, publication year	Study Objective Study design	Included studies	Results	Level of evidence Conclusions
			Other comparisons Two studies compared NaP with sodium picosulphate/magnesium citrate preparations. In one study, no difference was observed in quality of bowel preparation but the picosulphate regimen was better tolerated. In the second study, the NaP yielded significantly better bowel preparation and there was no difference in tolerability. Two further studies compared sodium picosulphate/magnesium citrate with PEG-based regimes. In one report PEG yielded superior bowel preparation with no difference in tolerability whilst in the second study there was no difference in efficacy but the picosulphate preparation was associated with superior tolerability. **Safety** No clinically significant complications were reported in any of the randomised controlled trials identified by this review. A number of studies recorded electrolyte changes before and after treatment. **Compliance** Compliance with bowel preparations, as evidenced by patients' ability to consume the complete prescribed treatment, was recorded in 18 of 25 studies comparing PEG with NaP. In all but one case more patients completed treatment with NaP than with PEG, although not all differences were statistically significant. Median completion rate for NaP was 97% (range 67–100%) vs. 89.5% for PEG (range 53–98%). No study explored the reasons behind these differences in a systematic fashion, although there is an common and reasonable assumption that it principally reflects high volumes normally associated with PEG. The relationship between treatment compliance and the efficacy of bowel preparation was not described in any of the studies.	

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	Medline, Embase, Cinnahl And Cochrane Central Databases databases: google scholar search engine; reference list of retrieved studies
	Date restriction	up to january 2006
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	Inclusion criteria: (i) randomised controlled trial; (ii) comparing two or more orally administered bowel preparation regimes; (iii) patients, undergoing colonoscopy; (iv) assessment of quality of bowel preparation using a categorical measure; (v) assessment of patient tolerability included; and (vi) results published in a peer review journal.
Validity assessment	Criteria and process used	**Quality assessment** of included studies performed; criteria reported
Data abstraction	Process used	Data abstracted by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	no
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Bini E.J, 2000	To compare patient tolerance, quality of preparation, and cost of 2 bowel cleansing regimens for flexible sigmoidoscopy. Prospective randomised, single-blind trial New York	250 patients undergoing screening flexible sigmoidoscopy were randomised to receive an oral preparation (group O: male gender 98.4%; mean age 66.4± 9.4) or enema preparation (group E: male gender 98.4%; mean age 66.2± 8.4) No significant difference between the two groups regard to age, gender and race.	Flexible sigmoidoscopy using the following bowel preparations: group O: 10 mg oral bisacodyl (1 h later) followed by 45 mL oral sodium phosphate solution with two 8 ounce glasses of water (n=126) or group E: 10 mg oral bisacodyl followed by 2 Fleet enemas 1 hour before leaving home the morning of the examination (n=124).	Patient tolerance, quality of preparation, nursing preparation time and cost, symptom score, depth of insertion, complications	<u>Patient tolerance </u>as easy or tolerable O 96.8% vs E 56.4% (p<0.001) <u>% patients completing the bowel preparation at home</u> O 100% vs E 73.4% (p<0.001) <u>Mean symptom score (0-39)</u> O 0.7±0.8 vs E 2.3±2.5 (p<0.001) No patient in either group had palpitations, chest pain or syncope during the preparation. <u>Preferer the same preparation</u> O 97.6% vs E 14.5% (p<0.001) <u>Quality of preparation</u>=good or excellent O 86.5% vs E 57.3% (p<0.001) <u>Mean depth of insertion (cm)</u> O 57.0±8.1 vs E 52.2±12.1 (p<0.001) <u>% complete sigmoidoscoopies</u> O 84.1% vs E 60.5% (p<0.001) <u>% patients at least 1 polyp detected</u> O 14.3% vs E 15.3% (p=0.82) One patient (group O) had a sigmoid adenocarcinoma detected. <u>Mucosal abnormalities (%)</u> O 23.8% vs E 15.3% (p=0.09) No mucosal ulcerations were seen in either group. One patient (group E) had a vasovagal episode after sigmoidoscopy that resolved with intravenous hydration. <u>Mean nursing preparation time(min)</u> O 34.6±25.4 vs E 65.3±43.5 (p<0.001) <u>Mean preparation cost</u> (medication and nursing costs-$) O 16.39±11.57 vs E 31.13±19.87 (p<0.001)	II An oral sodium phosphate preparation in combination with oral bisacodyl results in a superior quality endoscopic examination compared with an enema preparation for patients undergoing screening flexible sigmoidoscopy. This oral preparation is better tolerated, results in a more comprehensive endoscopic examination, and is more costeffective. By reducing the discomfort associated with the use of enemas, this oral preparation may improve patient acceptance of flexible sigmoidoscopy as a screening tool for colorectal cancer.

Quality assessment: allocation concealment: inadequate; blindness of provider: no; blindness of patients: yes; blindness of endoscopist: yes; blindness of outcome assessor: yes; None lost at follow up

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Fincher R.K., 1999	To compare three magnesium citrate sigmoidoscopy preparations in a randomised, single-blind, controlled trial. Randomised, single-blind controlled trial Washington, D.C. and Logan, Utah USA	291 outpatients undergoing flexible sigmoidoscopy were randomised to receive containing oral magnesium Citrate combinating with oral bisacodyl (group 1: 46.3% of males; mean age 60), one hypertonic phosphate enema (group 2: 49.5% of males; mean age 59.6), two hypertonic phosphate enemas (group 3: 50.5% of males; mean age 60.1). No significant difference among group 1, 2 and 3 with regard to gender, age, race, procedure indications, history of diabetes, diverticulos and polyps.	Flexible sigmoidoscopy using (as bowel preparations) the oral magnesium citrate (296 cc) in combination with: group 1: oral bisacodyl (10 mg), given with the magnesium citrate the night before the procedure (n=93); group 2: one hypertonic phosphate enema 1 h before the procedure; (n=97) group 3: two hypertonic phosphate enemas, given singly at 2 and 1 h before the procedure. (n=101).	Preparation quality, procedure duration, depth of endoscopic insertion, patient comfort and overall satisfaction	Quality ratings as excellent or good group 1 81% group 2 89% group 3 85% (p=0.30) Mean procedure duration (min) group 1 13 vs group 2 12.5 vs group 3 12.0 (p=0.63) Mean length of insertion (cm) group 1 54.8 vs group 2 56.5 vs group 3 56.6 (p=0.51) Polyps present (%) group 1 24.4 vs group 2 22.7 vs group 3 23.0 (p=0.96) Diverticuli present (%) group 1 35.6 vs group 2 32.0 vs group 3 30.0 (p=0.71) No differences in procedure discomfort and were equally likely to be willing to undergo repeat sigmoidoscopy in the future. Preparation tolerance (%) Easy: group 1 60 vs group 2 53.7 vs group 3 41.6 (p=0.032) Adverse effects no differences in the incidence of most side effects including nausea, vomiting, pain, cramping, and bloating, patients Diarrhea from preparation (any, %) group 1 80 vs group 2 67.7 vs group 3 52.5 (p=0.0003) Fully satisfied (%) group 1 91.4 vs group 2 92.8 vs group 3 95.0 (p=0.60) Repeat preparation required (%) due to poor preparation group 1 4.3 vs group 2 2.1 vs group 3 3.0 (p=0.66)	II There was no statistical difference between the quality of the three bowel preparations. Patients considered an oral bisacodyl and magnesium citrate regimen more easily tolerated, though it was associated with more diarrhea. The use of magnesium citrate and oral bisacodyl could also reduce nursing time. Such benefits could save overall clinic time and money.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of endoscopist: yes; blindness of outcome assessor: yes; 5 patients lost (3 from group 1, 1 from group 2 and 1 from group 3) at quality analysis due to violate blinding

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Atkin W.S., 2000	To compare the acceptability and efficacy of two methods of self administered bowel preparation for flexible sigmoidoscopy screening: a single phosphate enema and a single sachet of oral Picolax. Prospective randomised, single-blind trial UK	1,442 patients (undergoing screening flexible sigmoidoscopy were randomised to receive an oral laxative (group P) or a single phosphate enema (group E). No difference between the two centres for age and gender	Screening flexible sigmoidoscopy using the following bowel preparations: group E: a single self administered phosphate enema taken 1 h before leaving home for the examination (n=721) group P: a single sachet of oral sodium picosulphate with magnesium citrate taken at either 2 pm or 6 pm on the day before screening for a morning or afternoon examination respectively and no solid food (n=721).	Compliance, acceptability, adverse effects, quality of bowel preparation, complete examinations	**Compliance** (Total) E 84% *vs* P 79% No significant difference between the group E and P in the proportions who used an alternative bowel preparation (E 3% vs P 4%) **Acceptability** Willing to use same preparation again E 89% *vs* P 89% Ease of administration of enema Easy 78% (471) Very difficult or given by another person 2% (11) Felt unwell E 15% *vs* P 7% Abdominal pain or cramps E 9% vs P 10% Nausea or vomiting E 3% vs P 2% Faintness or dizziness E 4% vs P 3% Wind E 4% vs P 10% Bottom soreness E 14% vs P 9% Incontinence E 1% vs P 5% Sleep disturbance E 1% vs P 13% Adverse effects rated as moderate or severe after test: Bottom soreness E 11% vs P 6% (p<0.05) No differences between the preparations in the pain experienced during the test. Rates of wind, incontinence, and sleep disturbance were not higher in the group P on the morning after the test.	**II** The authors concluded the following: Based on the results of this study, we believe that a single, self administered enema is probably the best available preparation for flexible sigmoidoscopy screening

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					Efficacy Quality of bowel preparation: good or excellent E 76% vs P 65%) (p<0.001) Complete examinations E 83% vs P 76% Incomplete examinations due to poor bowel preparation E 7% vs P 10% No significant difference in polyp, adenoma and detection rates.	

Quality assessment: allocation concealment: adequate; blindness of provider: no (yes for consent for randomisation to different bowel preparation); blindness of patients: no, blindness of endoscopist: yes; blindness of outcome assessor: yes; 1 patient (from group E) lost at bowel preparation questionnaire before screening; 59 patients (24 from group E and 35 from group P) lost at questionnaire follow up after test.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Gidwani A.L., 2007	To compare two methods of bowel preparation with the current standard in an attempt to improve efficacy and acceptability. Prospective randomised, single-blind trial UK	Number of eligible patients:305 Number of enrolled patients: 261 261 outpatients undergoing flexible sigmoidoscopy were randomised to receive a single fleet enema (group 1: 50 men and 55 women; mean age 44.9±14.9), two fleet enemas (group 2: 36 men and 45 women; mean age 46.3±13.7) or lactulose and fleet enema (group 3: 40 men and 75 women; mean age 45.3±14.4). No significant difference among group 1, 2 and 3 with regard to gender (p=0.13) and age (p=0.81).	Flexible sigmoidoscopy using the following bowel preparations: group 1: one Fleet enema 2 h pre-procedure (n=105) group 2: two Fleet enemas, one on the evening prior to sigmoidoscopy and one 2 h preprocedure (n=81) group 3: oral lactulose 30 ml (48 and 24 h prior to the procedure) plus a single Fleet enema 2 h pre-procedure (n=75).	Patient acceptability to the preparation (by questionnaire), depth of insertion (adequate examinations), abnormalities noted, quality of bowel preparation	Ease of use (Likert scale): acceptable group 1 94.3% vs group 2 85.2% vs group 3 86.7% (p=0.09) Assistance required in using the preparation group 1 19.1% vs group 2 11.1% vs group 3 24% (p=0.11) Acceptable abdominal cramps group 1 83% vs group 2 85% vs group 3 72% (p=0.84) Prefer an alternative method (yes:no) No significant difference Mean depth of insertion (cm) group 1 51.5±19.9 vs group 2 57.6±20.2 vs group 3 55.2±17.9 (p=0.12) Quality of bowel preparation (% acceptable) group 1 83% vs group 2 88% vs group 3 73% (p=0.04) Statistical difference in the quality of preparation of patients in Group 2 vs Group 3 (p=0.02-Fisher's exact)	II The authors concluded the following: The addition of a Fleet enema or oral lactulose over and above a single Fleet enema gives no significant improvement in the acceptability or efficacy of bowel preparation. a single phosphate enema 2 h pre procedure is an effective method of bowel preparation for flexible sigmoidoscopy.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of endoscopist: yes; blindness of outcome assessor: unclear; 10 lost at follow up (Endoscopist questionnaire).

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Ruangsin S., 2007	To compare bowel preparation quality and patient tolerance of two common enema solutions for flexible sigmoidoscopy. Randomised, double-blind, controlled trial Thailand	300 patients were randomised to receive hypertonic sodium chloride enema (group C) or hypertonic sodium phosphate enema (group P).	Flexible sigmoidoscopy using the following bowel preparations: group C: hypertonic sodium chloride enema or group P: hypertonic sodium phosphate enema. Each enemas was administered 60 and 30 min before the procedure.	Preparation comfort, quality of the preparation by doctor	There were no serious complications during or following the procedures. Preparation quality as excellent or good C 76,9% vs P 72,9% (p=0,423) The hypertonic sodium chloride enema was associated with more abdominal discomfort (p = 0.018).	**II** Both enemas were safe for all patients with no statistical difference between the qualities of the two bowel preparations. Both preparations performed their bowel-cleaning function well and were suitable for the preparation of patients before flexible sigmoidoscopy. The less expensive hypertonic sodium chloride solution may be an option for hospitals where budgetary considerations are

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: yes; blindness of endoscopist: yes; blindness of outcome assessor: yes. None lost at follow up.

5.3   Length of endoscope

5.3.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 5

What is the difference in terms of quality (diagnostic yield), cost and side effects of short vs. longer scopes for FS screening?

PICOS

P: General population at average risk of CRC (age 50 or older) and individuals with a positive FOBT/FIT
I: Shorter scopes FS
C: Longer scopes
O: Diagnostic yield, cost, adverse effects
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

We performed a broad search on MedLine with the following strategy:
(exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy)

RESULTS

Three studies have been retrieved.

Fincher 2007 (1) performed a single blind randomised controlled trial comparing a standard 60-cm sigmoidoscope (diameter of 13.3 mm) with a thinner (diameter of 9.8 mm) 100-cm upper endoscope in 81 patients at average risk for colorectal cancer who performed flexible sigmoidoscopy. He found that patients who were treaded with longer and thinner scopes reported more comfort immediately after the procedure and 1 week later. The intubation time was significantly longer with the longer and thinner scope but the depth of insertion was significantly greater.

Friedland 2007(2) reported the results of three case series in which a new thinner device consisting of of a thin 9 mm scope, 170 cm in length, together with a 13 mm diameter 60 cm long overtube was used for colonoscopy. The first series consisted of 25 consecutive male patients who were scheduled for unsedated colonoscopy with the new device. The second series consisted of 75 consecutive male patients undergoing routine colonoscopy. An adult, pediatric and the thin scope/overtube were used in alternating cases. Patients were pre-medicated with lorazepam 2 mg sublingually (1 mg for patients over age 80) 15 min before the procedure. Intravenous fentanyl was administered if the patient requested further sedation.

The third series consisted of 35 patients who had incomplete colonoscopies in an endoscopy unit (the cecum was not reached) using any combination of standard adult (and/or pediatric endoscopes). In the comparative series, the new device seemed to be better tolerated by patients. In the third series composed of people in which colonoscopy has been incomplete using an adult or pediatric scope, the procedure was successful in 94%

Farraye 2004 (3) performed a single blind randomised controlled trial comparing a standard sigmoidoscope with diameter of 13.3 mm with an upper endoscope with a diameter of 9.8 mm in 160 women. The use of a standard upper endoscope for screening FS was associated with a more comfortable examination. Self-report scores for pain and discomfort were statistically lower in the women randomised to use of an upper endoscope for their screening FS. Additionally, there was a trend toward deeper insertion of the upper endoscope compared with the standard sigmoidoscope. These positive attributes were not associated with any increased risk of complications or decreased detection of polyps.

CONCLUSIONS

No studies were retrieved assessing the diagnostic yeld of longer vs shorter scopes.

The use of thinner scopes is associated with less pain and discomfort vs traditional scope in two RCTs (LEVEL OF EVIDENCE II)

In one uncontrolled series of patients who had an incomplete colonoscopy with a standard scope, the procedure was successful in 94% of patients with the use of a thinner scope (LEVEL EVIDENCE V)

REFERENCES

1. Fincher RK, Myers J, McNear S, Liveringhouse JD, Topolski RL & McNear J (2007), Comfort and efficacy of a longer and thinner endoscope for average risk colon cancer screening, *Dig.Dis Sci.*, vol. 52, no. 10, pp. 2892-2896.

2. Friedland S & Soetikno RM (2007), Small caliber overtube-assisted colonoscopy, *World J Gastroenterol.*, vol. 13, no. 44, pp. 5933-5937.

3. Farraye FA, Horton K, Hersey H, Trnka Y, Heeren T & Provenzale D (2004), Screening flexible sigmoidoscopy using an upper endoscope is better tolerated by women, *Am J Gastroenterol.*, vol. 99, no. 6, pp. 1074-1080.

5.3.2 Evidence tables

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
Fincher 2007	To assess patient comfort during nonsedated screening sigmoidoscopy with the use of a standard 60-cm sigmoidoscope compared with a thinner 100-cm upper endoscope randomised controlled trial	81 patients at average risk colorectal cancer. Patients with a history of colorectal cancer, large bowel resection, recent rectal bleeding, or severe cardiopulmonary disease were excluded. USA	Sigmoidoscopy Experimental intervention: upper endoscope was 100 cm in length and 9.8 mm in diameter control . 38 patients. Control intervention: standard sigmoidoscope was 60 cm in length and 13.3 mm in diameter. 43 patients	Patient comfort, abdominal pain, cramping, bloating, satisfaction, willingness to have the procedure done, procedure time, depth of insertion number of polyps	**Immediately after the procedure (mean, SD)** patient comfort longer and thinner 5.57 ± 2.13 standard 4.48 ± 2.36 P: 0.035 abdominal pain longer and thinner 3.13 ± 1.79 standard 3.87 ± 1.89 P: NS cramping longer and thinner 3.05 ± 1.90 standard 4.02 ± 1.68 P: 0.017 bloating longer and thinner 3.50 ± 1.52 standard 4.05 ± 1.44 P: NS satisfaction longer and thinner 5.55 ± 1.78 standard 5.88 ± 1.37 P: NS willingness to have the procedure done longer and thinner 1.11 ± 0.31 standard 1.14 ± 0.35 P: NS **1 week after the procedure (mean, SD)** patient comfort longer and thinner 4.91 ± 1.77 standard 3.90 ± 1.87 P: 0.015 abdominal pain longer and thinner 3.25 ± 2.07 standard 4.06 ± 1.92 P: NS cramping longer and thinner 2.96 ± 2.10 standard 3.38 ± 1.89 P: NS bloating longer and thinner 2.67 ± 1.64 standard 3.50 ± 1.90 P:0 .040 satisfaction longer and thinner 6.05 ± 1.47 standard 5.77 ± 1.84 P: NS	II The use of a thinner and longer endoscope is more comfortable than a standard sigmoidoscope. Although a 100-cm endoscope procedure takes longer to perform, it allows better evaluation of the colon and misses fewer adenomas.

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
					willingness to have the procedure done longer and thinner 1.13 ± 0.34 standard 1.12 ± 0.32 P: NS procedure time (min) longer and thinner 8.8 ± 3.3 standard 5.9 ± 2.1P: 0.001 depth of insertion (cm) longer and thinner 73.68 ± 19.92 standard 55.58 ± 7.65 P: 0.001 reaching splenic flexure (%) longer and thinner 76.32 standard 36.60 P: .001 patients with polyps longer and thinner 19 Standard 13.P: NS total polyps longer and thinner 27 Standard 20.P: NS	

Quality assessment: allocation concealment adequate. Blinding of providers: not possible; blinding of patients and outcome assessor (outcomes measured by self-reported questionnaire. None lost at follow up.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Friedland 2007	To feasibility of using a new thinner and scope for colonoscopy 3 case series	The first series consisted of 25 consecutive male patients who were scheduled for unsedated colonoscopy with the new device. The patients were scheduled for unsedated procedures because of patient preference, medical contraindications to sedation, or lack of a driver to take them home after the procedure. The second series consisted of 75 consecutive male patients undergoing routine colonoscopy An adult ,pediatric and the thin scope/overtube were used in alternating cases. Patients were pre-medicated with lorazepam 2 mg sublingually (1 mg for patients over age 80) 15 min before the procedure. Intravenous fentanyl was administered if the patient requested further sedation. The third series consisted of 35 patients who had incomplete colonoscopies in our endoscopy unit (the cecum was not reached) using any combination of standard adult and/or pediatric endoscopes. USA	The new colonoscopy system consists of a thin 9 mm scope, 170 cm in length, together with a 13 mm diameter 60 cm long overtube	Caecal intubation rate Maximum pain level (scale 1-10) Median duration of the procedure complication	**First series** Caecal intubation rate: 100% Median maximal pain level :3 Median duration of the procedure: 13 min Complication: 1 bleeding 1 week after a polypectomy **Second series** Completion rate without additional sedation Adult device: 36% Pediatric device: 56% New device: 96% Mean dose of fentanyl (μg) used Adult device: 51 Pediatric device: 39 New device: 12 Median maximal pain level Adult device: 8 Pediatric device: 7.5 New device: 3.5 Caecal intubation rate: 100% in all groups Median time to reach the cecum (min) Adult device: 6 Pediatric device: 4 New device:5.5 **Third series** Caecal intubation rate: 94% Median time to reach the cecum (min) :7 Complication: 0	**V** Small caliber overtube-assisted colonoscopy is less painful than colonoscopy with standard adult and pediatric colonoscopes. Male patients could undergo unsedated colonoscopy with the new system with relatively little pain. The new device is also useful for most patients in whom colonoscopy cannot be completed with standard instruments.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Farraye 2004	To assess satisfaction in women undergoing screening FS using an upper endoscope (E, diameter 9.8 mm) *versus* a standard sigmoidoscope (S, diameter 13.3 mm) randomised controlled trial	160 asymptomatic women undergoing screening FS. Patients with gastrointestinal symptoms of rectal bleeding, abdominal pain, weight loss, etc. were excluded. USA	Sigmoidoscopy Experimental intervention: n.82 Upper endoscope was 9.8 mm in diameter Control intervention: n.83 standard sigmoidoscope 13.3 mm in diameter.	Patient self-report of satisfaction depth of insertion of the igmoidoscope, polyp/cancer detection, duration of the procedure, any complications	Overall satisfaction scale Upper: 1.6 ± 0.4 standard: 1.6 ± 0.4 P:NS Pain and discomfort scale upper: 1.9 ± 0.9 Standard: 2.3 ± 0.9 P: 0.006 depth of insertion (cm) upper : 54.5 ± 9.2 standard : 51.6 ± 10.3 P: 0.05 duration of the procedure (min) upper : 7.3 ± 4.0 standard : 5.6 ± 2.9 P: 0.003 complication: upper : 2.5% standard: 1.2% P: NS polyp detection: upper:18.3% standard: 10.2% P:NS	II The use of a standard upper endoscope for screening FS was associated with a more comfortable examination. Self-report scores for pain and discomfort were statistically lower in the women randomised to use of an upper endoscope for their screening FS. Additionally, there was a trend toward deeper insertion of the upper endoscope compared with the standard sigmoidoscope. These positive attributes were not associated with any increased risk of complications or decreased detection of polyps.

Quality assessment: allocation concealment adequate. Blinding of providers: not possible; blinding of patients and outcome assessor (outcomes measured by self-reported questionnaire. None lost at follow up.

5.4 Equipment modalities and completion rates

5.4.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 6

Do the following modalities improve completion rates in lower GI endoscopy:
- Variable stiffness instruments,
- MR tracking devices
- Wire guided techniques

PICOS

P: General population at average risk of CRC (age 50 or older) and individuals with a positive FOBT/FIT
I: FS and colonoscopy with variable stiffness instruments, MR tracking devices, wire guided techniques
C: FS and colonoscvopy without these modalities
O: Detection rates
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

In the first instance systematic reviews were searched on MedLine and Embase. Then primary studies and narrative reviews were considered. All searches were performed in August 2008.
Pubmed
The following search terms produced five papers on variable stiffness instruments and magnetic imaging / tracking devices:
Search term: 'variable stiffness colonoscopes' produced 27 results and four relevant papers.
Search term 'magnetic endoscope imaging and colonoscopy performance' produced 5 results and one relevant paper.
The following search terms were used to identify papers on wire guided techniques on both MedLine and Embase (no relevant papers were found):
'wire guided colonoscopy and completion'
'wire guided colonoscopy'
'wire guided techniques AND colonoscopy'
'wire guided colonoscopy AND completion rates'

RESULTS

No systematic reviews were found. Three studies were found on variable stiffness colonoscopes and magnetic imaging devices. One was a narrative literature review and the others were RCTs. No articles were found pertaining to wire-guided techniques.

Narrative reviews

Subramanian & Rex 2003 (1) evaluated the literature prior to 2003. A total of 12 articles and abstracts were included, 9 of which were RCTs; for the other included studies study design was not specified. All compared variable stiffness colonoscopy with adult colonoscopy. Most of the studies showed that variable stiffness did not affect caecal intubation rate and caecal intubation time, whereas two studies showed that it reduced the caecal intubation rate achieved by less experienced examiners. The authors concluded that there was no convincing evidence to suggest that variable stiffness contributes to improved rates of caecal intubation and thus completion rates.

Shah 2002 (2) was already included in the review of Subramanian & Rex for the first part of the study assessing the effectiveness of variable stiffness. Here are considered only the results relating to the use of MEI imaging when using variable stiffness. The study shows that stiffening was significantly more effective when used in combination with magnetic endoscope imaging (69% with imager vs. 45% without imager; p = 0.0102).

Shah et al, 2000 (3) assessed the effect of MEI on colonoscopy performance of trainees and experienced endoscopists, comparing for each group the intubation times, the number of attempts at straightening the colonoscope, the completion rates and the duration of looping. The study fund that MEI significantly improves performance of colonoscopy, particularly when used by trainees, or by experts in technically difficult cases; loops were straightened or controlled effectively, resulting in quick intubation times and high completion rates.

CONCLUSIONS

Variable stiffness has not been proven to consistently improve caecal intubation rate and caecal intubation time (LEVEL OF EVIDENCE I). From 2 RCTs MEI view seems to improve performances of endoscopists both with variable stiffness colonoscopy and with traditional colonoscopy (LEVEL OF EVIDENCE II)

REFERENCES

1. Subramanian S & Rex DK (2003), Variable stiffness colonoscopes: do they offer a better examination?, *Curr.Opin.Gastroenterol.*, vol. 19, no. 5, pp. 492-496.

2. Shah SG, Brooker JC, Williams CB, Thapar C, Suzuki N & Saunders BP (2002), The variable stiffness colonoscope: assessment of efficacy by magnetic endoscope imaging, *Gastrointest.Endosc.*, vol. 56, no. 2, pp. 195-201.

3. Shah SG, Brooker JC, Williams CB, Thapar C & Saunders BP (2000), Effect of magnetic endoscope imaging on colonoscopy performance: a randomised controlled trial, *Lancet*, vol. 356, no. 9243, pp. 1718-1722.

5.4.2 Evidence tables

Author, publication year	Review Objective	Included studies	Outcomes	Results	Level of evidence Conclusion
Subramanian & Rex 2003	This review evaluates the most recent literature pertaining to variable stiffness colonoscopes in the context of previously published data. Narrative review.	12 papers two of which in abstracts form 4934 patients included 9 studies are RCTs comparing variable stiffness colonoscopy vs adult colonoscopy. The other studies made the same comparison but the study design is not specified	Caecal intubation rate Caecal intubation time Ancillary maneuvers pain	Caecal intubation rate: 6 studies (5 of which RCTs) found non significant difference; the other did not assess this outcome Caecal intubation time: 7 studies (four of which RCTs) found no significant difference; 5 studies (2 RCT) found significant less time with variable stiffness Pain: 4 studies (2 RCTs) found no significant diffence; 4 studies (3 RCTs) found significant less pain with variable stiffness	I In summary, the most consistent advantage for variable stiffness colonoscopes has been a reduction in the need for ancillary maneuvers. There is no convincing evidence that variable stiffness increases caecal intubation rates, and the role of variable stiffness in previously incomplete colonoscopies has not yet been adequately evaluated. In experienced colonoscopists' hands, variable stiffness appears to have little or no impact on the caecal intubation time. However, in less experienced hands, there is likely a slight reduction in caecal intubation time with variable stiffness, and this effect becomes more marked as the level of colonoscopy experience decreases.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	Not reported
	Date restriction	Not reported
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	Not reported
Validity assessment	Criteria and process used	Not done
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	no
Study characteristics	Type of studies, participants, interventions, outcomes	no
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	No
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results presented narratively

Author, publication year	Study Design	patients	outcomes	Results	Conclusions
Shah et al. 2002	RCT Variable stifnees colonoscopy with or without the endoscopist viewing the magnetic endoscope imaging display UK	175 patients undergoing routine colonoscopy excluding any with previous colonic resection 88 with the MEI view 87 without this view	Efficacy of the variable-stiffness device in preventing recurrent colonoscope looping, or counteracting looping sufficiently to facilitate advancement of the colonoscope tip.	Insertion tube stiffness was increased one or more times in 53% (47/88) of examinations carried out with the aid of the MEI system, and in 68% (59/87) of examinations performed without the MEI view. Stiffening was used with similar frequency in patients examined with and without the magnetic endoscope imaging view. Stiffening was significantly more effective when used in combination with magnetic endoscope imaging (69% with imager vs. 45% without imager; $p = 0.0102$).	II The study clearly demonstrates the benefits of using imaging to enhance the effect of the variable stiffness modality, by allowing optimal straightening of the colonoscope before stiffening. When combined with MEI, the stiffening function of the VSC was effective 69% of the time, compared with only 45% of the time when used without imaging.

Quality assessment: unclear allocation concealment; blindness of provider not possible; blindness of patients and outcome assessor not specified. All patients completed the study

Author, publication year	Study Design	Study Participants	Outcomes	Results	Conclusions
Shah et al. 2000	RCT. Group 1 Trainees examined 113 consecutive patients. MEI views were recorded in all examinations, but procedures were randomised to be done either with the imager view the imager display (n=58), or without (n=55). Group 2 2 skilled endoscopists were randomised (as with group 1) to undertake consecutive examinations (n=183) either with (n=92) or without (n=91) the MEI view. MEI views of all procedures were analysed retrospectively. UK	Group 1 (trainees) 113 consecutive patients undergoing colonoscopy 58 patients with the magnetic image view, 55 patients without the magnetic imager view Group 2 (experts) 183 consecutive patients undergoing colonoscopy 92 patients with the magnetic image view 91 patients without this view.	*Intubation times* *Number of attempts at straightening the colonoscope* *completion rates* *duration of looping*	*Intubation times* Group 1 With MEI view: median 11·8 min [4·3–31·5] Without 15·3 min [4–67] Group 2 With MEI view 8·0 min [2·6–40·8] Without 9·3 min [2·5–52·6] *Number of attempts at straightening the colonoscope* Group 1 With MEI view median 5 [0–20] Without 12 [0–57] Group 2 With MEI view 7 [0–55] Without 10 [0–80] *Colonoscopy completion rates* Group 1 vs Group 2 With MEI view 100% Without 89% *duration of looping* With MEI view median 3 min [0–18·8] Without 5·4 min [0–44·5])	II MEI significantly improves performance of colonoscopy, particularly when used by trainees, or by experts in technically difficult cases; loops were straightened or controlled effectively, resulting in quick intubation times and high completion rates.

Quality assessment: unclear allocation concealment; blindness of provider not possible; blindness of patients and outcome assessor not specified. All patients completed the study.

5.5 Visualisation techniques and detection rates

5.5.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 7

Do the following modalities improve high risk lesion detection rates in lower GI endoscopy:
- dye spraying
- NBI
- autofluorescence

PICOS

P: General population at average risk of CRC (age 50 or older) and individuals with a positive FOBT/FIT
I: FS and colonoscopy with dye spraying, NBI, autofluorescence
C: FS and colonoscopy without these modalities
O: High risk lesion detection rates
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

MedLine and Embase searches were performed since 2000
Search terms:
 'narrow band imaging AND colonoscopy' OR 'narrow band imaging AND colonoscopy AND detection rates'. 'autofluorescence AND colonoscopy': 'chromoscopy AND colonoscopy'.

We performed also a broader search on MedLine with the following strategy:
(exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy)
The Cochrane Library
Searches on this website identified one systematic review relating to chromoscopy

RESULTS

NBI
7 papers relating to narrow band imaging (NBI) were found: one narrative review (1), 2 randomised controlled trials (2,3), 2 diagnostic accuracy study (4,5) and 1 prospective study (6) and one randomised trial (7) comparing diagnostic accuracy of magnified chromoendoscopy and magnified NBI
The American Society for Gastrointestinal Endoscopy (ASGE) (1) performed a narrative review on the accuracy of NBI and multi-band imaging as part of a Technology Status Evaluation Report in 2008. The review included five studies, two of which were RCTs. Three, prospective comparative studies

totalling 245 patients, demonstrated that NBI was superior to standard white-light endoscopy (WLE) for polyp differentiation. NBI appears to be useful for differentiating colonic polyps in terms of vascular pattern intensity and pit pattern characteristics.

Diagnostic accuracy for distinguishing adenomas:
- NBI: 87 – 93%
- ICC: 91 – 93%
- WLE: 67 – 82%

However, the 2 randomised controlled trials included in the review that compared NBI with wide-angle HRE during colonoscopy withdrawal did not show a statistically significant difference in the detection rate of adenomas. Rex and Helbig, 2007 performed a randomised controlled trial comparing white light endoscopy with NBI. All examinations were performed by an experienced endoscopist with a known high adenoma detection rate. The findings of this study did not show a better detection of adenomas by NBI by an endoscopist with a known high adenoma detection rate compared to white light endoscopy. Adler et al. 2008, performed a prospective randomised study to evauate NBI with conventional colonoscopy, comparing the difference in the adenoma detection rate. Adenomas were detected more frequently in the NBI group (23%) than the control group (17%), although this difference was not significant (p=0.129). Adler et al, also speculate as to whether the increased adenoma detection rate seen with NBI may have been caused by a training effect of better polyp recognition on NBI.

The authors concluded that NBI may enhance the diagnosis and characterisation of mucosal lesions in the GI tract, particularly as adjunctive techniques to magnification endoscopy. Standardisation of image characterisation, further image-to-pathology correlation and validation, and the impact of these technologies on patient outcomes are necessary before endorsing the use of NBI and MBI in the routine practice of GI endoscopy.

Inoue et al. 2008 (2) performed a randomised controlled trial to determine the efficacy of the pan-colonic NBI system in adenoma detection. 243 patients were randomised to either the pan-colonic NBI system or to conventional colonoscopy. The pan colonic system significantly increased the total number of adenomas detected and the number of diminutive adenomas without prolongation of extubation time. The authors concluded that routine use of the pan-colonic NBI system for diminutive adenomas may be recommended.

Kaltenbach 2008(3) performed a randomised controlled trial comparing NBI with white light colonoscopy on the neoplasms miss rate in 284 adult patients referred for colonoscopy. He didn't find a statistically significant difference in the neoplasm miss rate and in the detection rate between the two procedures.

Katagiri 2008 (4) performed a cross-sectional study to assess the diagnostic accuracy of NBI to distinguish lesions with low degree dysplasia and lesions with high degree dysplasia/cancer in 104 consecutive patients with 139 colorectal lesions. Sensitivity and specificity of NBI, using standard colonoscopy as reference standard, were 90.3% and 97.1% respectively. There were several limitations in this study. First, as this was a pilot study, all the lesions were evaluated by a single endoscopist (Y.S.) who had broad experience of NBI with magnification. The learning curve and interobserver∕intra-observer validation of capillary patterns should be clarified in further prospective studies. Moreover the interpretation of both test results was not blinded. Author concluded that The capillary patterns observed by NBI with magnification provide high accuracy for distinction between LGD and HGD∕ invasive cancer, and thus can be used to predict the histopathology of colorectal neoplasia in vivo. Further prospective studies are necessary to clarify the learning curve and interobserver∕intraobserver validation of capillary patterns observed by this diagnostic modality.

Rastogi 2008 (6) performed a prospective study to determine the detection rate of additional polyps by NBI after removal of polyps visualized by standard white light colonoscopy (WLC) on 40 patients at average-risk screening for colon cancer. 41% additional polyps were detected that were missed by WLC. However, the study has many limitations: First and foremost, it is a pilot feasibility study involving a relatively small number of patients, and definitive conclusions cannot be drawn from such

a study design. Patients were not randomised to either standard or NBI colonoscopy, and it is possible that the 40% additional polyps could have also been detected by a second standard colonoscopy. Also, the second look with NBI may have been associated with additional cleansing efforts of the segment as a result of the prior evaluation by WLC. The possibility of ascertainment bias also cannot be excluded Authors concluded that whether NBI is superior to standard colonoscopy needs to be tested in multicenter, randomised, controlled trials for the detection of polyps and predicting their histologic diagnoses

SU 2006 (5) performed a diagnostic accuracy study comparing sensitivity and specificity of conventional colonoscopy, NBI and chromoendoscopy in differentiating neoplastic and non neoplastic lesions in 110 colorectal polyps in 78 consecutive patients. Histological diagnosis was used as reference standard. NBI (Sensitivity 95.7% Specificity 87.5%) was as effective as chromoendoscopy using indigo carmine contrast dye (Sensitivity 95.7% Specificity 87.5%), and both modalities are significantly better than conventional colonoscopy (Sensitivity 82.9% Specificity 80%).

Tischendorf 2007 (7) performed a randomised controlled trial to directly compare the diagnostic values of chromoendoscopy and NBI for the differentiation of neoplastic from non−neoplastic colorectal polyps. 99 patients with 200 colorectal polyps identified by conventional colonoscopy were randomised by alternation to NBI with magnification, or chromoendoscopy with magnification. Using the Kudo classification of mucosal patterns, NBI with magnification resulted in a sensitivity of 90.5% and a specificity of 89.2% for the differentiation of neoplastic vs. non−neoplastic lesions. This performance was comparable to magnifying chromoendoscopy with a sensitivity of 91.7% and a specificity of 90%, respectively. Using vascular patterns for differentiation, NBI with magnification correctly identified 93.7% of neoplastic polyps and 89.2% of nonneoplastic colorectal lesions, whereas magnifying chromoendoscopy had a specificity of 95% but a sensitivity of only 66.7 %. Authors concluded that NBI in combination with magnifying endoscopy is a promising tool for the differentiation of neoplastic from non−neoplastic colorectal polyps in vivo without the necessity of using dye. The detection of capillary vessels with NBI allows the evaluation of colorectal lesions based on the vascular patterns with high diagnostic accuracy

3 papers on **AUTOFLUORESENCE ENDOSCOPY** were found:

McCallum et al. 2008 (8), a prospective diagnostic accuracy study, evaluated whether autofluoresence colonoscopy can facilitate endoscopic detection and differentiation of colorectal polyps compared to WL colonoscopy in 107 paients. When using an AIR with the empirical cut-off value of 2.3, AF endoscopy had a sensitivity of 85% and a specificity of 81% in distinguishing adenomatous polyps from hyperplastic polyps, a positive predictive value (PPV) of 92%, and a negative predictive value (NPV) of 68%. The sensitivity of the system was found to be 76% for polyps <5 mm, 100% for polyps 5 to 10 mm, and 92% for polyps >10 mm. This study showed a striking visual distinction between adenomatous and hyperplastic polyps suggesting that autofluoresence may be a promising enhancement for conventional colonoscopy.

Matsuda et al. 2008 (9) conducted a randomised controlled trial with 167 patients randomised to receive colonoscopy with WL after colonoscopy with AFI, or colonoscopy with AFI after colonoscopy with WL. The miss rate for all polyps was 30% (AFI) and 49% (WL); P:0.01. The miss rate of neoplasia was 29% (AFI) and 47% (WL); P:0.02. The authors concluded that AFI detects more polyps in the right-sided colon compared to WL endoscopy.

Mayinger 2008 (10) performed a small pilot study on 12 patients with known or highly suspected colonic adenoma or carcinoma. The study was aimed to determine the feasibility of obtaining selective fluorescence of precancerous/cancerous lesions in the colon with a new fluorescence video endoscope system in combination with the selective photosensitizer precursor hexaminolevulinate (HAL), and to carry out a dose-finding study with evaluation of the optimal dose and application time. Using histological findings as the gold standard, 52/53 of the premalignant/malignant lesions showed red fluorescence under the photodynamic diagnosis (PDD) examination; 38/53 were detected with white−light endoscopy. The PDD mode showed 28% more polyps than did white−light endoscopic imaging. Authors concluded that administration of HAL enema induces selective fluorescence and

increases the lesion detection rate in patients with colorectal adenoma and early carcinoma. Further investigations with larger groups of patients are needed to corroborate the present data.

CHROMOSCOPY

6 studies were retrieved: a systematic review including randomised controlled trials comparing chromoendoscopy with conventional colonoscopy (11), two diagnostic accuracy (12,5) studies comparing sensitivity and specificity of chromoendoscopy and conventional colonoscopy in differentiating neoplastic vs non neoplastic lesions, a prospective study (13) comparing the detection rate of chromoendoscopy and conventional sigmoidiscopy in the same group of patients, one randomised trial (14) comparing the diagnostic accuracy of magnified chromocolonsocpy and conventional chromocolonosocpy and one randomised trial (7) comparing diagnostic accuracy of magnified chromoendoscopy and magnified NBI.

A Cochrane systematic review by Brown et al, 2007 (11) was included which evaluated whether the use of chromoscopy enhances detection of polyps and neoplasia compared with conventional endoscopy. It included four prospective randomised trials. Chromoscopy detected significantly more polyps (WMD 0.77 (CI 0.52-1.01)) and neoplastic lesion (WMD 0.35 (CI 0.23-0.47)) than conventional endoscopy. There was also a statistically significant difference in the number of patients with at least 1 polyp (OR 2.13 (CI 1.47-3.10) or 1 adenoma (OR 1.61 (CI 1.24-2.09). detected. The authors concluded that there is strong evidence that chromoscopy enhances the detection of neoplasia in the colon and rectum. Patients with neoplastic polyps, particularly those with multiple polyps, are at increased risk of developing colorectal cancer. Such lesions, which presumably would be missed with conventional colonoscopy, could contribute to the interval cancer numbers on any surveillance programme. However, the time constraints involved in incorporating routine pan-chromoscopy suggest selective use may be the only feasible practical application. Authors concluded that two groups of selected patients could benefit form chromoscopy use: one was the chronic inflammatory bowel disease group on surveillance for premalignant change (dysplasia); the other is people with genotypically or phenotypically proven Hereditary Non-Polyposis Colorectal Cancer (HNPCC).

Pohl 2008 (12) performed a diagnostic accuracy study comparing sensitivity and specificity of chromoendoscopy with conventional colonoscopy in low- and high-magnification modes in differentiating neoplastic and non neoplastic polyps with 63 patients with 150 flat or sessile lesions less than 20 mm in diameter. Histological diagnosis was used as reference standard. He found that chromoendosocpy is superior to conventional colonoscopy in predicting polyp histology. Magnification further improves the sensitivity and diagnostic accuracy.

Ratiu 2007 (13) performed a prospective study comparing the detection rate of conventional sigmoidoscopy and chromoendosocpy in a series of 55 patients who were analysed by both the procedures. Chromoendoscopy identified significantly more lesions than sigmoidioscopy, particularly small lesions (<5 mm) hyperplastic polyps and inflammatory/non specific lesions.

Emura 2007 (14) performed a randomised trial comparing the diagnostic accuracy of magnified chromocolonoscopy and conventional chromocolonoscopy in 170 patients with lesions ≤ 100 mm. Two pathologists blinded to the endoscopic findings examined the retrieved tissues. The overall accuracy of magnifying chromocolonoscopy for differentiating neoplastic lesions (95%, 135 of 142), was significantly higher than that of conventional chromocolonoscopy (84%, 102 of 122; P <0.01). The accuracy of magnifying chromocolonoscopy for differentiating neoplastic lesions ≤5 mm was 94% (87of 93), whereas that of conventional chromocolonoscopy was only 78% (69 of 89; P <0.001).

CONCLUSIONS

The use of autofluoresence seems to result in better detection rates than conventional endoscopy (LEVEL OF EVIDENCE II).

There is strong evidence that chromoscopy enhances the detection rate of neoplasia in the colon and rectum. In particular, chromoscopy is likely to yield significantly more patients with at least one neoplastic lesion and significantly more patients with three or more neoplastic lesions. However, the

time constraints involved in incorporating routine pan-chromoscopy suggest selective use may be the only feasible practical application (LEVEL OF EVIDENCE I).

For chromoscopy the diagnostic accuracy studies also found better accuracy than conventional colonoscopy in distinguishing between neoplastic and non-neoplastic lesions. One study also found better detection rate with use of chromosigmoidoscopy (LEVEL OF EVIDENCE III).

The results about NBI were inconclusive with three randomised trials reporting that the detection rates of adenomas were not significantly different from that of conventional endoscopy and one finding better results for NBI (LEVEL OF EVIDENCE II).

The results of diagnostic accuracy studies showed better accuracy than standard colonoscopy in differentiating between neoplastic and non neoplastic lesions (LEVEL OF EVIDENCE III).

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5.5.2 Evidence tables

Author, publication year	Study Objective Study design	Inclusion criteria	Results	Summary
ASGE 2008	Technology Status Evaluation Report on the accuracy of Narrow band imaging (NBI) and Multi-Band Imaging (MBI) Narrative Review	Controlled clinical trials are emphasized, but in many cases data from randomised controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used.	NBI vs standard white-light endoscopy (WLE) Included studies: 5, 2 of which were RCTs Three prospective, comparative studies totalling 245 patients and 333 colorectal lesions have demonstrated NBI and indigo carmine chromoendoscopy (ICC) to be superior to standard white-light endoscopy (WLE) for polyp differentiation on the basis of imaging characteristics. The diagnostic accuracies for NBI, ICC, and WLE were 87% to 93%, 91% to 93%, and 67% to 82%, respectively, for distinguishing adenomas from nonadenomatous lesions. One RCT compared white light endoscopy with NBI. All examinations were performed by an experienced endoscopist with a known high adenoma detection rate. The findings of this study did not show a better detection of adenomas by NBI by an endoscopist with a known high adenoma detection rate compared to white light endoscopy. The second RCT evaluated NBI with conventional colonoscopy, comparing the difference in the adenoma detection rate. Adenomas were detected more frequently in the NBI group (23%) than the control group (17%), although this difference was not significant (p=0.129). Adler et al, also speculate as to whether the increased adenoma detection rate seen with NBI may have been caused by a training effect of better polyp recognition on NBI.	**II-III** NBI and MBI may enhance the diagnosis and characterisation of mucosal lesions in the GI tract, particularly as adjunctive techniques to magnification endoscopy. Standardisation of image characterisation, further image-topathology correlation and validation, and the impact of these technologies on patient outcomes are necessary before endorsing the use of NBI and MBI in the routine practice of GI endoscopy.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	medline, maude (food and drug administration center for devices and radiological health) database. technical data are gathered from traditional and web-based publications, proprietary publications, and informal communications with pertinent vendors
	Date restriction	up to September 2007
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	Controlled clinical trials are emphasized, but in many cases data from randomised controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used.
Validity assessment	Criteria and process used	Not done
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	No
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results presented narratively

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Inoue et al. 2008	determine the efficacy of the pancolonic NBI system in adenoma detection. Randomised controlled trial	243 patients who underwent total colonoscopy at the Osaka Medical College Endoscopy Center; patients with positive FOBT or symptoms Japan	Experimental intervention: pancolonic NBI Control intervention: standard colonoscopy	Mean extubation time n. of patient with at least one polyp n. of polyps identified n. of patients with at least one adenoma n. of adenomas identified n. of patients with at least one diminutive adenoma (<5 mm) n. of diminutive adenomas (<5 mm) identified	control group: 121 patients (73 men; mean age, 61.1 ± 13.5 years), NBI group:122 patients (77 men; mean age, 62.9 ± 11.3 years). No statistically significant differences between the control group and NBI group with respect to age, gender, quality of bowel preparation or indications for colonoscopy. Extubation time NBI: 528 ± 128 s Control: 512 ± 176 s. P: ns n. of patients with at least one polyp: NBI: 51% Control: 39% P:0.06 N. of polyps identified: NBI: 127 Control:.78 P:0.01 n. of patients with at least one adenoma NBI: 42% Control:34% P:0.2 n. of adenomas identified: NBI: 102 Control: 65 P:0.04 n. of patients with at least one diminutive adenoma (<5 mm) NBI: 30% Control: 17% P:0.01 n. of diminutive adenomas NBI: 53 Control: 26 P: 0.02	II The authors concluded that the pan-colonic NBI system improves the total number of adenomas detected, including significantly more diminutive adenomas, without prolongation of extubation time. These results indicate that routine use of the NBI system for surveillance of diminutive adenomas may be recommended

Quality assessment: allocation concealment: adequate; Randomisation was revealed to the endoscopist on intubation of the caecum; blindness of patients not relevant; none lost at follow up; blindness of pathologist (outcome assessor) not specified

Author, publication year	Study Objective Study Design	Study Participants	Outcomes	Results	Conclusions
McCallum et al. 2008	To evaluate whether autofluorescence (AF) colonoscopy can facilitate endoscopic detection and differentiation of colorectal polyps. Each section of the rectum was visualized by using both AF and WL modes. Visible pathology was recorded, and biopsy specimens were taken Diagnostic accuracy study (prospective) UK	107 Patients scheduled for a colonoscopy were evaluated with both AF and white-light (WL) colonoscopy. .	Specificity, sensitivity and predictive values were calculated using histopathology determination as the criterion standard. Colonscopist were asked to macroscopically differentiate hyperplastic polyps from adenoamtous polyps	A total of 75 polyps were detected: 54 adenomatous and 21 hyperplastic polyps. Both adenomatous polyps and hyperplastic polyps had similar appearances with WL, but, when viewed with AF, the adenomatous polyps were redder in appearance, with higher AF readings . The AF mode detected all polyps; however, the WL mode failed to detect 3 polyps histologically confirmed as tubular adenomatous polyps. Colorectal adenomas had a significantly higher AF intensity ratio (AIR) compared with hyperplastic polyps (median, interquartile range): adenoma (3.54, 2.54-5.00] versus hyperplastic (1.60, 1.30-2.24); P <.0001). When using an AIR with the empirically cut-off value of 2.3, AF endoscopy had a sensitivity of 85% and a specificity of 81% at distinguishing adenomatous polyps from hyperplastic polyps, a positive predictive value (PPV) of 92%, and a negative predictive value (NPV) of 68% . The sensitivity of the system was found to be 76% for polyps <5 mm, 100% for polyps 5 to 10 mm, and 92% for polyps >10 mm Colonoscopist macroscopic differentiation of hyperplastic from adenomatous polyps under WL: sensitivity : 64%, specificity: 100%, PPV of 100%), and a NPV of 40% Sensitivity of 47% for polyps <5 mm and 100% for polyps 5 to 10 mm and those >10 mm.	III The authors concluded that this study showed a striking visual distinction between adenomatous and hyperplastic polyps when using AF colonoscopy. These results suggest that AF is a promising candidate for further development and study.

Quality assessment: spectrum of patients representatives of the patients who will receive the test in practice; no clear description of patients selection criteria; possible verification bias: reference standard (histopathology) only for positive; clear description of index test, comparator and reference standard; no withdrawn form the study; index test results interpreted without knowledge of the results of the reference standard.

Author, publication year	Study Objective Study Design	Study participants	interventions	Outcomes	Results	Level of evidence Conclusions
Matsuda et al. 2008	To evaluate whether autofluorescence imaging (AFI) system can detect more colorectal polyps than WL. Randomised controlled trial	167 patients undergoing colonoscopy; excluded patients with previously detected polyps or with a history of surgical resection of the proximal colon	Experimental intervention: autofluorescence imaging (AFI) colonoscopy Control intervention: WL colonoscopy. group A underwent colonoscopy with WL after colonoscopy with AFI, and group B underwent colonoscopy with AFI after colonoscopy with WL	N. of detected lesions n. of neoplastic detected lesions characteristics of missed lesions	Group A: 83 Group B: 84 Total number of polyps detected: AFI = 100 WL = 73 Miss rate for all polyps AFI :30% WL 49% (P = 0.01). Total n. of neoplastic lesions detected: AFI:92 WL:69 Miss rate of neoplastic lesions: AFI: 29% WL: 47% (P:0.02) Characteristics of the missed neoplastic lesions flat elevated: AFI:14 (74%) WL:39 (87%), small (≤5 mm): AFI18 (95%) WL 41 (91%) low-grade dysplasia : AFI 19 (100%) WL 45 (100%),	**II** AFI detects more polyps in the right-sided colon compared to WL colonoscopy. AFI videoendoscopy system is useful for the detection of right-sided colonic polyps, especially flat and/or diminutive adenomatous lesions compared to conventional (WL) colonoscopy. In the near future, multicenter trials should be performed to validate the usefulness of this system.

Quality assessment: allocation concealment unclear; blindness of endoscopist not possible; blindness of patients not relevant pathologists who were completely blinded to each endoscopic diagnosis evaluated all pathological specimens; none lost at follow up.

Author, publication year	Study Objective Study design	Included studies	Outcomes	Results	Level of evidence Conclusion
Brown et al. 2007	To determine whether the use of chromoscopy enhances detection of polyps and neoplasia during endoscopic examination of the colon and rectum. Cochrane systematic review	4 RCTs	Primary outcomes: N. of polyps detected per patient with each intervention (including neoplastic and non-neoplastic lesions) N. of neoplastic polyps (adenomas/carcinomas) detected per patient with each intervention. N. of patients with at least 1polyp (neoplastic and nonneoplastic) detected with each intervention N. of patients with at least 1 neoplastic polyp (adenoma/carcinoma) detected with each intervention

Secondary outcomes: N. of diminutive neoplastic (adenoma/carcinoma) polyps (<5mm) detected per patient with each intervention N. of patients with at least 1 diminutive neoplastic (adenoma/carcinoma) polyp (<5mm) detected with each intervention N.of patients with more than 3 neoplastic (adenoma/carcinoma) polyps detected with each intervention Extubation time Site of the lesions found (right verses left colon/rectum) | N. of polyps (neoplastic and non-neoplastic) detected was highly significantly greater for chromoscopy in all studies and when the studies were combined (WMD 0.77 (CI 0.52-1.01)). This enhanced yield was maintained even if neoplastic lesions only were considered (WMD0.35 (CI 0.23-0.47)). N. of patients with at least one polyp: significant difference in favour of the chromoscopy group (OR 2.13 (CI 1.47-3.10) N. of patients with at least one neoplastic lesions (OR 1.61 (CI 1.24-2.09)

N. of diminutive neoplastic lesions was significantly in favour of chromoscopy: (WMD (fixed) 0.27 (CI 0.14-0.40) n.of patients with at least 1 diminutive neoplastic lesion: OR 1.71 (CI 1.23-2.37 n.. of patients with 3 or more neoplastic lesions was more than twice as likely to be detected using chromoscopy: (OR (fixed) 2.55 (CI 1.49-4.36). | I

There appears to be strong evidence that chromoscopy enhances the detection of neoplasia in the colon and rectum.

Patients with neoplastic polyps, particularly those with multiple polyps, are at increased risk of developing colorectal cancer. Such lesions, which presumably would be missed with conventional colonoscopy, could contribute to the interval cancer numbers on any surveillance programme. |

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE, EMBASE AND THE COCHRANE LIBRARY; HAND SEARCH OF ABSTRACTS FROM RELEVANT MEETINGS.
	Date restriction	up to October 2006
	any restriction	No restriction
Selection	Inclusion and exclusion criteria	Randomised controlled trials comparing chromoscopic with conventional endoscopy for the detection of polyps in adults
Validity assessment	Criteria and process used	Quality assess performed using validated checklist
Data abstraction	Process used	Two authors independently entracte data and assess quality
Quantitative data synthesis	Measures of effect, method of combining results	Reported; heterogeneity assessed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Katagiri 2008	To investigate if NBI with magnification could help predict the histology of early colorectal neoplasia. diagnostic accuracy cross-sectional study	A series of 104 consecutive patients with 139 colorectal lesions. Patients with polyps that had been biopsied previously were excluded. Patients with inflammatory bowel disease, familial polyposis or hereditary nonpolyposis colorectal cancer were also considered ineligible Japan	Experimental NBI Reference standard: colonoscopy. A standard videoendoscopic system with two light sources was used for examination. One light source was for the standard optical filter (broadband) and the other was for the NBI system. The NBI system is based on modification of spectral features with each optical filter narrowing a bandwidth of spectral transmittance, as described previously. The button on the control section of the colonoscope immediately allows single-touch exchange between the conventional view and the NBI view	Sensitivity and specificity in distinguishing LGD vs HGD/cancer lesions	Sensitivity: 90.3% Specificity: 97.1%	**III** The capillary patterns observed by NBI with magnification provide high accuracy for distinction between LGD and HGD∕invasive cancer, and thus can be used to predict the histopathology of colorectal neoplasia in vivo. Further prospective studies are necessary to clarify the learning curve and interobserver∕intraobserver validation of capillary patterns observed by this diagnostic modality

Quality assessment: Prospective recruitment. Spectrum of patients representatives of the patients who will receive the test in practice. Patients selection criteria clearly described. The whole sample received the reference standard (avoidance of verification bias). Execution of the index test and reference standard clearly described. Index test and reference standard results interpreted with knowledge of the other test results. There were several limitations in this study. First, as this was a pilot study, all the lesions were evaluated by a single endoscopist (Y.S.) who had broad experience of NBI with magnification. The learning curve and interobserver∕intra-observer validation of capillary patterns should be clarified in further prospective studies. Moreover the interpretation of both test results was not blinded.

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
Kaltenbach 2008	To compare the NBI with white light colonoscopy in the neoplasm miss rate Randomised controlled trial	284 consecutive adult patients who were referred for elective outpatient colonoscopy Patients with known inflammatory bowel disease, personal or family history of polyposis syndrome, or referred for evaluation of a known lesion were excluded USA	Experimental intervention: NBI: n.142 Control intervention: white light colonoscopy:n: 142 In the NBI group, endoscopists completed the first examination with NBI and an immediate second examination using WL. In the control WL group, endoscopists performed both examinations using WL.	Neoplasms miss rate Repeat colonoscopy used as reference standard Any identified lesion at the time of initial detection was removed such that the endoscopist performed the second examination in a colon putatively cleared of lesions. Hence, a "missed" lesion was defined as one identified during insertion or withdrawal of the second examination. Neoplasm miss rates was calculated using both patient and neoplasm based analyses. Secondary end points included neoplasm detection rates, completion of examinations, and complications. A detected lesion was defined as a lesion identified during the first examination.	Patient Neoplasm miss rate Any adenoma NBI. 12.6% White light 12.1% Risk difference: 0.5% (95%C I-7.2 to 8.3) ≤5 mm NBI: 10.4% White light: 9.2% Risk difference: 1.2% 95%CI (-5.9 to 8.2) 6-9mm NBI: 2.2% White light: 2.8% Risk difference: -0.6% (-4.3 to 3.1) ≥ 10mm NBI: 0.7% White light: 0.0% Risk difference: 0.5% (95%CI -0.7 to 2,2) Missed lesions with NBI showed similar characteristics to those missed with WL. All missed neoplasms were tubular adenomas, the majority (78%) was (5 mm and none were larger than 1 cm (one-sided 95% CI up to 1%). Nonpolypoid lesions represented 35% (13/37) of missed neoplasms	II NBI did not improve the colorectal neoplasm miss rate compared to WL; the miss rate for advanced adenomas was less than 1% and for all adenomas was 12%. The neoplasm detection rates were similar high using NBI or WL.

Quality assessment: allocation concealment: adequate. It was not possible to blind the endoscopist to the imaging intervention, and, logistically, it was not possible to have a different endoscopist perform the second examination. blindness of patients not relevant; 8 patients excluded from the analysis, 7 from the NBI group and 1 from the white light group.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Rastogi 2008	To determine the detection rate of additional polyps by NBI after removal of polyps visualized by standard white light colonoscopy (WLC) and to correlate the surface mucosal and vascular patterns with polyp histologic diagnosis. prospective pilot feasibility study	40 consecutive adult patients who were referred for elective outpatient colonoscopy Inclusion criteria were average-risk screening for colon cancer.. The exclusion criteria were prior surgical resection of any portion of the colon, inflammatory bowel disease, use of antiplatelet agents or anticoagulants that precluded removal of polyps during olonoscopy, poor general condition or any other reason to avoid prolonged procedure time, and prior history of colon polyps. USA	Experimental intervention: NBI: Control intervention: white light colonoscopy: The colonoscope was inserted to the cecum by using standard white light. On withdrawal, the cecum and the ascending colon were initially examined with white light, and all visualized polyps were removed. The colonoscope was then advanced again to the cecum. Subsequently, the cecum and the ascending colon were reexamined by NBI. All additional polyps then visualized by NBI were removed. The remaining portions of the colon were evaluated in a similar fashion in 15- to 20-cm segments, initially by standard white light followed by NBI, and polyps were removed.	Polyp detection rate of polyps missed by WLC	Seventy-two polyps were detected with WLC With use of NBI, an additional 51 polyps were detected (ie, missed by WLC). 41% additional polyps were detected that were missed by WLC	**III** This pilot study demonstrates the feasibility of polyp detection by NBI. Despite the promising results of this study, several limitations of the study and technique merit mention. First and foremost, it is a pilot feasibility study involving a relatively small number of patients, and definitive conclusions cannot be drawn from such a study design. Patients were not randomised to either standard or NBI colonoscopy, and it is possible that the 40% additional polyps could have also been detected by a second standard colonoscopy. Also, the second look with NBI may have been associated with additional cleansing efforts of the segment as a result of the prior evaluation by WLC. The possibility of ascertainment bias also cannot be excluded. This study was conducted in a veteran male population and thus the results may not be generalisable.. Whether NBI is superior to standard colonoscopy needs to be tested in multicenter, randomised, controlled trials for the detection of polyps and predicting their histologic diagnoses.

Quality assessment: Prospective cohort study. Spectrum of patients representatives of the patients who will receive the test in practice. Patients selection criteria clearly described. The whole sample received the reference standarad (avoidance of verification bias) . Execution of the index test and reference standard clearly described. Index test and reference standard results interpreted with knowledge of the other test results

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Pohl 2008	To compare the accuracy of FICE, standard colonoscopy, and conventional chromoendoscopy with indigo carmine in low- and high- magnification modes in differentiating neoplastic and non neoplastic polyps diagnostic accuracy study	Sixty-three patients with 150 flat or sessile lesions less than 20 mm in diameter were enrolled Germany	FICE conventional chromoendoscopy with indigo carmine Standard colonosocpy At colonoscopy, all detected lesions that met the inclusion criteria were observed in six different endoscopic modalities; after observation by standard colonoscopy, the system was switched over to the FICE mode by one touch of the control knob to examine the vascular network carefully. Finally, indigo carmine (0.2%) was sprayed directly on the mucosa surface for pit pattern analysis. In each setting, the lesion was observed in low- and high-(50- to 100-fold) magnification modes and pictures were recorded electronically. After observation, all polyps were resected or biopsied for histological analysis reference standard: histological diagnosis	Sensitivity Specificity in differentiating neoplastic and non neoplastic polyps	**Sensitivity** Low magnification Conventional colonoscopy 76.4% (CI95% 65.1% - 84.9%) Chromoendoscopy: 91% (CI95% 82.9% - 95.6%) High magnification Conventional colonoscopy: 84.3% (CI95% 74.8–90.6) Chromoendoscopy 95.5% (CI95% 88.7–98.3 **Specificity** Low magnification Conventional colonoscopy 65.6% (CI95% (51.7–77.2%) Chromoendoscopy: 67.2% (CI95% 50.1–80.7%) High magnification Conventional colonoscopy: 64% (CI95% 47.8–77.4 Chromoendoscopy 73.8% (CI95% 59.6–84.3)	**III** Chromo-endoscopy is superior to conventional colonoscopy in predicting polyp histology. Magnification further improves the sensitivity and diagnostic accuracy

Quality assessment: Prospective recruitment. Spectrum of patients not representatives of the patients who will receive the test in practice. Patients selection criteria clearly described. The whole sample received the reference standard (avoidance of verification bias) . Execution of the index test and reference standard clearly described. Index test and reference standard results interpreted without knowledge of the other test results.

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
Ratiu 2007	to evaluate if indigo carmine significantly improves the detection of adenomas in the distal colon and rectum and, consequently, whether Chromo-endoscopy could become routine procedure in flexible sigmoidoscopy screening prospective comparative study	55 patients were enrolled . Exclusion criteria were: absence of a written consent, pregnancy, coagulation disorders with high risk for gastrointestinal bleeding, already diagnosed colorectal inflammatory diseases, adenomas or carcinoma Germany	Conventional sigmoidoscopy Chromoendoscopy During the first examination in a standard view, all detected protruding lesions were classified with regard to size (category I: <3 mm; category II: 3- 5 mm; category III: >5 mm) and position (cm from anal verge). The second sigmoidoscopy was performed by an examiner blinded for the results of the first one. 15- 20 ml of 0.27% indigo carmine solution was applied on the entire examined colorectal mucosa. Thereby, all protruding mucosal changes were classified again using the same criteria and then were endoscopically removed. Two experienced pathologists independently classified the findings as adenomas, hyperplastic polyps or other lesions (inflammatory or non-specific changes). Dysplasia in adenomas was divided into low and high grade according to the Vienna classification	Detection rate	Total n of lesions detected: Conventional sigmoidoscopy: 104 in 30 patients Chromoendoscopy: 373 in 47 patients Lesion <3 mm sigmoidoscopy: 70 Chromoendoscopy: 306 P<0.001 Lesion 3-5 mm sigmoidoscopy: 20 Chromoendoscopy: 47 P<0.001 Lesion >5mm sigmoidoscopy: 14 Chromoendoscopy: 20 Hyperplastic polyps sigmoidoscopy: 66 Chromoendoscopy: 215 P<0.001 Adenomas sigmoidoscopy: 16 Chromoendoscopy: 27 P<0.001 Inflammatory/non specific sigmoidoscopy: 22 Chromoendoscopy: 131 P<0.001	III Chromoendoscopy with indigo carmine during flexible sigmoidoscopy was safe, less complicated, but relatively prolonging the extubation time. After staining, significantly more lesions were identified, mostly hyperplastic polyps and inflammatory/non-specific lesions. Regarding adenomas, chromoendoscopy significantly improved the detection of polyps <5 mm. Thus, routine indigo carmine application in flexible sigmoidoscopy screening could become a good option, especially when colonoscopy is unavailable or not accepted by the patient.

Quality assessment: Prospective cohort study. Characteristics of patients not described. Patients selection criteria not described. The whole sample received the reference standarad (avoidance of verification bias) . Execution of the index test and reference standard clearly described. Index test and reference standard results interpreted without knowledge of the other test results.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Emura 2007	To validate the effectiveness of magnification chromo-endoscopy compared to conventional chromo-endoscopy for the diagnosis of neoplastic colorectal polyps in the setting of a health testing center. Randomised controlled trial	Five hundred asymptomatic average-risk subjects. Exclusion criteria were history of colorectal cancer or colonic surgery, familial adenomatous polyposis, acute inflammatory bowel disease and anticoagulation therapy. Japan	Experimental intervention: magnification chromocolonoscopy Control intervention.: chromocolonoscopy In both groups, lesions diagnosed as non-neoplastic were left *in situ* and advanced carcinomas were biopsied. Both these lesion types were excluded from analysis. Two pathologists blinded to the endoscopic findings examined the retrieved tissues. Hyperplastic polyps, inflammatory polyps and juvenile polyps were categorized as non-neoplastic lesions. Adenomas were categorized as lowgrade dysplasia (LGD) or high-grade dysplasia (HGD) on the basis of degree of atypia. Lesions with mild or moderate atypia were classified as LGD, and lesions with severe atypia or noninvasive carcinoma classified as HGD.	N. of lesion detected Diagnostic accuracy in differentiating neoplastic and non neoplastic lesion	Of the 500 screened subjects, 192 (38%) had clinically significant lesions: 170 patients with polyps ≤10 mm were included in the study, <u>n. of lesion detected</u> magnification chromocolonoscopy: 142 chromocolonoscopy :122 <u>overall accuracy for differentiating neoplastic lesions</u> magnifying chromocolonoscopy :95%, (135 of 142), conventional chromocolonoscopy :84%, (102 of 122) *P* <0.01. <u>accuracy for differentiating neoplastic lesions ≤5 mm</u> magnifying chromocolonoscopy 94% (87 of 93) conventional chromocolonoscopy 78% (69 of 89) *P* <0.001.	II MCC is more effective than conventional chromo-colonoscopy for diagnosing neoplastic colorectal polyps; MCC should be used routinely for screening colonoscopy even in health check-up medical centers..

Quality assessment: allocation concealment: unclear; blinding of providers: not possible; blinding of patients: not relevant; blinding of outcome assessor: yes. None lost at follow up. Only patents with lesions ≤10 mm were included in the study, Not specified how they were allocated to groups.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Su 2006	To analyse the NBI system for its ability to differentiate between neoplastic and nonneoplastic colorectal polyps and compared its performance with that of conventional colonoscopy and chromoendoscopy using a 0.2% indigo carmine contrast technique diagnostic accuracy study	110 colorectal polyps in 78 consecutive patients who underwent colonoscopy. The indications for colonoscopic examination were colorectal cancer screening, postpolypectomy follow-up, bowel habit changes, and body weight loss. Taiwan	Experimental test : NBI , chromocolonoscopy, convetional colonoscopy Reference standard : Histological diagnosis During the procedure, conventional colonoscopy first detected lesions, and then the NBI system was used to examine the capillary networks. Thereafter indigo carmine (0.2%) was sprayed directly on the mucosa surface prior to evaluating the crypts using a conventional colonoscope. The pit patterns were characterized using the classification system proposed by Kudo. Finally, a polypectomy or biopsy was performed for histological diagnosis.	Sensitivity Specificity in differentiating neoplastic and non neoplastic lesions	Conventional colonoscopy Sensitivity 82.9% (CI95% 71.6–90.4) Specificity 80% (CI95% 63.9–90.4) NBI Sensitivity 95.7% (CI95% 87.2–98.9) Specificity 87.5% (CI95% 72.4–95.3) Chromoendoscopy Sensitivity 95.7% (CI95% 87.2–98.9) Specificity 87.5% (CI95% 72.4–95.3)	II For the differential diagnosis of neoplastic and nonneoplastic colorectal lesions, NBI is as effective as chromoendoscopy using indigo carmine contrast dye, and both modalities are significantly better than conventional colonoscopy...

Quality assessment: Prospective recruitment study. Spectrum of patients representatives of the patients who will receive the test in practice. Patients selection criteria clearly described. The whole sample received the reference standard (avoidance of verification bias) . Execution of the index test and reference standard clearly described. Index test and reference standard results interpreted without knowledge of the other test results.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Tischendorf 2007	To directly compare the diagnostic values of chromoendoscopy and NBI for the differentiation of neoplastic from non−neoplastic colorectal polyps. randomised controlled trial	210 patients underwent magnifying conventional colonoscopy. Patients with adenomatosis coli, coagulopathy, insufficient bowel preparation, or previous colonoscopy within the last 3 years (except for patients who were sent for polypectomy of known polyps) were excluded from the study. In 99 of the 210 patients, 200 colorectal polyps were detected and consecutively distributed in a 1:1 ratio either to magnifying chromoendoscopy or to NBI magnification Germany	Experimental intervention: n.47 Chromoendoscopy with magnification Control intervention: n.52 NBI with magnification.	Per lesion Sensitivity and Specificity in the differentiation of neoplastic from nonneoplastic colorectal polyps According to pit pattern classification and according to vascular patterns	According to pit pattern classification Conventional colonoscopy Sensitivity 63.4% Specificity 51.9% Chromoendoscopy wit magnification Sensitivity 91.7% Specificity 90% NBI with magnification Sensitivity 90.5% P: NS Specificity 89.2% P:NS according to vascular patterns Conventional colonoscopy Sensitivity 47.2% Specificity 97.4% Chromoendoscopy wit magnification Sensitivity 66.7% Specificity 95% NBI with magnification Sensitivity 93.7% P<0.001 Specificity 89.2% P:NS	II Using the Kudo classification of mucosal patterns, NBI with magnification resulted in a sensitivity of 90.5% and a specificity of 89.2% for the differentiation of neoplastic vs. non−neoplastic lesions. This performance was comparable to magnifying chromoendoscopy with a sensitivity of 91.7% and a specificity of 90%, respectively. Using vascular patterns for differentiation, NBI with magnification correctly identified 93.7% of neoplastic polyps and 89.2% of nonneoplastic colorectal lesions, whereas magnifying chromoendoscopy had a specificity of 95% but a sensitivity of only 66.7 %. NBI in combination with magnifying endoscopy is a promising tool for the differentiation of neoplastic from non−neoplastic colorectal polyps in vivo without the necessity of using dye. The detection of capillary vessels with NBI allows the evaluation of colorectal lesions based on the vascular patterns with high diagnostic accuracy.

Quality assessment: allocation concealment inadequate. None lost at follow up. All test results interpreted without knowledge of other test and histological diagnosis results. All patients received reference standard. Absence of verification bias. Patients representative of patients who could receive the test in practice.

5.6   Carbon dioxyde insufflation

5.6.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 8

Does carbon dioxide insufflation improve patient tolerance and reduce complications?

PICOS

P: General population in need of flexible sigmoidoscopy or colonoscopy
I: Carbon dioxide insufflation
C: Room air insufflation
O: Pain and discomfort during and after the flexible sigmoidoscopy/colonoscopy; risk of explosion during polypectomy, same day barium enema/CT colonography
S: RCTs, systematic and narrative reviews, randomised controlled trials, cohort and case control studies

SEARCH METHOD

MedLine and Embase searches were performed for systematic reviews in the first instance and then for primary studies. Searches were restricted to between 2000 and 2008.
MedLine
Mesh terms: ("Carbon Dioxide"[Mesh] AND "Insufflation"[Mesh]) AND "Colonoscopy"[Mesh] identified 16 results and 4 relevant papers.
The following Mesh terms returned no relevant results:
("Carbon Dioxide"[Mesh] AND "Insufflation"[Mesh]) AND "Pain"[Mesh]) AND "Enema"[Mesh])
("Carbon Dioxide"[Mesh] AND "Insufflation"[Mesh])) AND "Sigmoidoscopy"[Mesh]
We also performed a broader search on MedLine with the following strategy: (exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy)
No further papers of interest were returned on Embase.

RESULTS

5 randomised controlled trials were found. No systematic reviews were located.

Church 2003 (1) evaluated carbon dioxide insufflation in a randomised controlled trial. 247 patients were randomised to either the air group or the carbon dioxide group. Pain scores immediately after the examination and completion rates did not show any significant differences between the groups. Pain scores 10 minutes after the examination showed that patients in the carbon dioxide group experienced less pain than the air group. This study concluded that carbon dioxide offers a more comfortable experience to patients undergoing colonoscopy.

Sumanac et al, 2002 (2) tested a new commecially available carbon dioxide delivery system in a double blind randomised trial. Patients were randomised to undergo colonoscopy with carbon dioxide or with air. Postprocedural pain at 1 and 6 hours was less in the carbon dioxide group than the air group: 7% and 9% versus 45% and 31% respectively. At 1 and 6 hours after colonoscopy the CO_2 group reported significantly less passage of flatus than the air group This study demonstrated higher patient tolerance in those patients receiving carbon dioxide insufflation.

Bretthauer 2002a (3) compared pain associated with carbon dioxide insufflation versus air insufflation in 230 patients undergoing flexible sigmoidoscopy in the NORCCAP study using a randomised controlled double blind design. The amount of discomfort was significantly reduced in the carbon dioxide group 1, 3 and 6 hours after flexible sigmoidoscopy. No difference was found during the exam and 24 hours after the examination. The authors concluded that carbon dioxide reduces post-examination discomfort.

Bretthauer 2002b (4) also examined whether CO_2 insufflation reduced pain after the examination compared with air insufflation in 240 patients undergoing colonoscopy in the NORCCAP study using a double blind randomised controlled design. There were statistically significant differences in pain scores, favouring CO_2 insufflation at all observed time points after examination. Moreover no rise in the ETCO2 was found during the exam. The author concluded that CO_2 insufflation is safe and produces less discomfort after the exam than air insufflation.

Wong 2008 (5) assessed if CO_2 insufflation reduce pain during and after the procedure compared to air insufflation in a single blind randomised trial. There was a statistically significant difference favouring CO_2 during the procedure and 30 minutes after the procedure. 1 and 2 hours after, the results favoured CO_2 but did not reach the statistical significance. Authors concluded that because of better tolerance, colonoscopy with CO_2 insufflation might gain wide acceptance in the community to be used as a screening tool

CONCLUSIONS

All the retrieved studies observed a reduction in discomfort during and post-examination in patients insufflated with carbon dioxide compared with air insufflation both in the FS and the colonoscopy examination (LEVEL OF EVIDENCE I).

REFERENCES

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5. Wong JC, Yau KK, Cheung HY, Wong DC, Chung CC & Li MK (2008), Towards painless colonoscopy: a randomised controlled trial on carbon dioxide-insufflating colonoscopy, *ANZ.J.Surg.*, vol. 78, no. 10, pp. 871-874.

5.6.2 Evidence tables

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
Church 2003	To assess whether carbon dioxide insufflation would reduce post colonoscopy discomfort Randomised, controlled trial	247 patients presenting for colonoscopy Body mass index, completion rate, and pattern of sedation and analgesia were similar for the two groups . Although there were more females in the CO2 group, hysterectomy rates were the same.. There were no significant differences between the groups for indications for colonoscopy, findings, and procedures performed.	Experimental intervention: carbon dioxide insufflation:123 patients. Control group: air insufflation: 124 patients	Pain measured on a ten-point analog scale (0 : no pain, 10 : worst imaginable pain) immediately after the examination had been completed and ten minutes later. .Patient satisfaction measured on a ten-point analog scale1: completely unsatisfied; 10: completely satisfied.	Amounts of sedation or analgesia used: mo significant differences., % of examinations completed: Air: 98.4 %; carbon dioxide:95.2 %, Patient satisfaction: Air: 9.4; carbon dioxide, 9.5). Pain scores immediately after the examination: air: 4.3 carbon dioxide 3.6 NS 10 minutes later air: 2.1 carbon dioxide 0.9 ($P \_ 0.05$,).	II This study has shown that patients having colonoscopy with CO2 as the insufflating gas had less abdominal pain ten minutes after the examination had ended than a group of similar patients whose insufflating gas was air. Use of carbon dioxide as an insufflating agent offers a more comfortable experience to patients undergoing colonoscopy. The present study suggests that it may be a particular advantage in the training setting, whereas others have encouraged its use particularly in cases of ischemic colitis, diverticulitis, irritable bowel syndrome, and inflammatory bowel disease. It is cheap, safe, and logistically straightforward to arrange.

Quality assessment: allocation concealment: unclear. Patients randomised to different room for examination where different insufflation was performed. Two endoscopists with different experience participated in the study; it is not clear if the two colonoscopist performed the exam always in the same room or not. If yes, this could introduce bias because one group had the examination performed by the less experienced and the other by the more experienced endoscopist.The study was unblinded to the endoscopists, research staff, and endoscopy assistants, but patients were not informed about which gas was being used until all data had been collected; none lost at follow up; blindness of outcome assessor (patient self-reported score).

Author, publication year	Study Objective Study Design	participants	interventions	outcomes	Results	Conclusions Level of evidence
Sumanac et al. 2002	To compare the effects of CO2 and air insufflation on residual bowel gas and postprocedure pain Randomised controlled double blind study	100 patients referred for elective colonoscopy because of family history or personal history of polyps. Patients with active GI bleeding, symptoms caused by inflammatory bowel disease, or a history of colonic resection were excluded.	CO_2 insufflation:49 Air insufflation:51	Pain immediately after the procedure ,1, 6 and 24 hour after using a 5 point scale: 1: none, 5 extreme Flatus passage 1, 6. 24 hors after the procedure on a 5 point scale; 1: none, 5 extreme	Of the 100 patients recruited, 97 completed the study; Pain after colonoscopy was significantly less in the CO_2 group at 1 hour and at 6 hours ($p < 0.0001$). In the air group, 45% and 31% of subjects had "mild," "moderate," or "severe" pain at 1 and 6 hours, respectively, compared with 7% and 9%, respectively, in the CO_2 group. There was also a trend toward reduced pain scores in the CO_2 group immediately after colonoscopy, although this did not reach significance ($p < 0.07$). Pain scores at 24 hours were minimal and essentially the same in the 2 groups ($p < 0.40$). At 1 and 6 hours after colonoscopy the CO_2 group reported significantly less passage of flatus than the air group ($p < 0.001$ No complications resulted from use of the CO_2 delivery system.	**II** Insufflation of CO_2 rather than air significantly reduces abdominal pain and bowel distension after colonoscopy. CO_2 may be insufflated safely and effectively with the new CO_2 delivery system..

Quality assessment: allocation concealment: unclear; double blind study; blindess of outcome assessor (patient self reported score); three patients in the CO2 group did not complete the procedure, one because of the discovery of a obstructing rectal tumour, one because of inadequate bowel preparation and one because of extreme pain before the start of the procedure, and this was thought to be a potential source of bias with respect to post-procedural pain score.

Author, publication year	Study Objective Study Design	Study Participants	intervention	outcomes	Results	Conclusions Level of evidence
Bretthauer 2002a	The aim of the present study was to evaluate whether carbon dioxide insufflation reduces discomfort during and after flexible sigmoidoscopy for colorectal cancer screening. Randomised controlled double blind trial	230 consecutive participants in an ongoing FS screening trial for the prevention of CRC (NORCCAP, Norwegian Colorectal Cancer Prevention) Participants in NORCCAP are men and women, 50–64 years of age, randomly drawn from the population registry.	Experimental group: Carbon dioxide insufflation for FS Control group: air insufflation for FS One experienced colonoscopist performed all the procedures	Abdominal discomfort : 100-mm visual analogue scale (VAS) bounded at the left end by 'no abdominal discomfort' and at the right end by 'discomfort as severe as it could be' measured at 1,2,6,24 hour after the examination	Participant without any discomfort at 1 hour Air: 64% CO_2: 84% P:0.006 3 hours Air: 62% CO_2: 80% P:0.01 6 hours Air :64% CO_2.:78% P:0.01 24 hours Air:90% CO_2:90% Discomfort during the examination: no statistically significant difference	**II** The use of carbon dioxide instead of air insufflation significantly reduces the amount of post-examination discomfort. The use of CO_2 rather than air insufflation could lead to better public acceptance for FS screening.

Quality assessment: adequate allocation concealment; double-blind study; blindness of outcome assessor (patient self reported score); 11 patients in the air group and 7 in the CO2 group were withdrawn from the analysis because of incomplete questionnaire or questionnaire not returned.

Author, publication year	Study Objective Study Design	Study Participants	Intervention	Outcomes	Results	Conclusions Level of evidence
Bretthauer 2002b	The aim of the present study was to evaluate whether carbon dioxide insufflation reduces pain during colonoscopy compared with air and if leds to a rise in the body CO_2 level Randomised controlled double blind trial	267 NORCCAP participants referred for colonoscopy	Experimental group: Carbon dioxide 121 patuentsinsufflation for colonoscopy Control group: air insufflation for colonoscopy: 119 patients One experienced colonoscopist performed all the procedures	Abdominal discomfort : 100-mm visual analogue scale (VAS) bounded at the left end by 'no abdominal discomfort' and at the right end by 'discomfort as severe as it could be' measured at 1,2,6,24 hour after the examination End-tidal (ET) CO_2 as a method for expressing arterial CO_2	249 patients completed the questionnqire; 10 patients (7 in the air group and 3 in the CO_2 group received sedation and were excluded from the analysis. Results presented for 240 patients There were statistically significant differences in pain scores, favouring CO_2 insufflation at all observed time points after examination. The overall mean difference was 7.8 mm (95% CI 4.4–11.2) ($p<0.001$). The pain reduction after examination was significantly more rapid in the CO2 group ($p=0.003$). The maximum difference (14 mm (95% CI 9–19); $p<0.001$) was observed one hour after the examination. ETCO2 : no rise in ETCO2 during or after the examination in any group. On the contrary, we observed a significant reduction in ETCO2 levels during examination in both groups ($p<0.001$). This reduction was more pronounced when air was used.	II CO_2 insufflation is safe during colonoscopy with no rise in ETCO$_2$ level. CO$_2$ was found to be superior to air in terms of pain experienced after the examination..

Quality assessment: adequate allocation concealment; double blind study; blindness of outcome assessor (patient self reported score); 11 patients in the air group and 7 in the CO2 group were withdrawn form the analysis because of incomplete questionnaire or questionnaire not returned.

Author, publication year	Study Objective Study Design	Participants	Interventions	Outcomes	Results	Conclusions Level of evidence
Wong 2008	To compare the effects of CO_2 and air insufflation on pain during and after the procedure Randomised controlled double blind study Hong Kong	96 patients referred for elective colonoscopy. Patients with severe chronic obstructive pulmonary disease requiring long-term medication; patients with previous history of colectomy; patients with suboptimal mental status for pain scores assessment; and patients with active gastrointestinal bleeding or intestinal obstruction requiring colonoscopic lavage during examination were excluded	CO_2 insufflation:46 Air insufflation:50	Pain during and after the examination using a visual analogue scale. Caecal intubation rate Time to reach the caecum Complication. Patients' satisfaction and acceptance of the procedure assessed with questionnaire	Pain during procedure (VAS) Mean (SD) CO_2 2.34 (0.42) Air 4.16 (0.40) P <0.01 Pain 30 min after procedure (VAS) Mean (SD) CO_2 0.59 (0.19) Air 1.37 (0.27) P: 0.02 Pain 1 h after procedure (VAS) Mean (SD) CO_2 0.16 (0.10) Air 0.39 (0.15) P: 0.16 Pain 2 h after procedure (VAS) Mean (SD) CO_2 0.09 (0.05) Air 0.18 (0.08) P: 0.53 Caecal intubation rate (%) CO_2 96% Air 98% Median caecal intubation time in min (range) CO_2 6 (3–25) Air 7 (3–22). No complication occurred in the CO_2 i group, whereas one patient in the AIRi group developed late haemorrhage 5 days after polypectomy Patients' satisfaction and acceptance of the procedure: no significant difference	**II** Insufflation with CO_2 during colonoscopy results in less pain during and after the examination. Because of better tolerance, colonoscopy with CO_2 insufflation might gain wide acceptance in the community to be used as a screening tool

Quality assessment: allocation concealment: adequate: sealed envelopes; single-blind study; blindness of outcome assessor (patient and independent assessor blinded); for three patients the examination was incomplete because of looping of the colonoscope, two in the CO2 and one in the air group.

5.7   Conscious vs. deep sedation

5.7.1   Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 9

What are the benefits and risks of conscious versus deep sedation?

PICOS

P: Patients with a positive screening test using another modality (FlexSig, FOBT, CTC)
I: Conscious sedation
C: Deep sedation; no sedation
O: Adverse effects, cecum intubation/completion rate, detection rate, pain and discomfort, satisfaction
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

MedLine and Embase searches were performed for systematic reviews in the first instance and then for primary studies, restricted to papers published between 2000 and 2008.
Search terms: 'sedation AND colonoscopy AND systematic review' returned one systematic review published in 2008 on moderate sedation.

Free text search terms: 'deep sedation AND colonoscopy AND risks' returned 6 results. None of these were deemed relevant.

Cochrane Library was also searched looking at the reviews of the Colorectal cancer review group

RESULTS

Two systematic reviews on moderate sedation and 1 prospective study on deep sedation were found:
McQuaid et al, 2008 (1) performed a systematic review of RCTs on moderate sedation for colonoscopy and upper endoscopy. 36 studies were included. Studies were selected if they compared outcomes of moderate sedation between at least 2 active study arms or 1 active study arm and 1 placebo or no sedation study arm. Meta-analyses were performed on a total of 17 studies deemed to have similar end points. Applicability of the results on colonoscopy is limited by the fact that only 12 out of 36 studies were on colonoscopy and that comparison has been done considering studies in upper endoscopy and colonoscopy together. Moreover the marked variability in study design, methodologic quality, regimens tested, and outcomes assessed in the included studies limited the ability to define an "optimal" moderate sedation regimen. Pooling results from multiple studies was particularly problematic because of differences among studies in the centers, patient populations, geographic locations, physician practices, endoscopic techniques, methods and levels of sedation, and measurement of sedation end points. None of the included studies compared sedation versus no sedation in colonoscopy. The majority of included trials compared different kinds of moderate sedation

between each other. Sedation improved patient satisfaction (RR 2.29, range 1.16-4.53) and willingness to repeat upper endoscopy (RR 1.25, range 1.13-1.38) versus no sedation. Midazolam provided superior patient satisfaction to diazepam (RR Z1.18, range 1.07-1.29) and less frequent memory of upper endoscopy (RR 0.57, range 0.50-0.60) versus diazepam. Adverse events and patient/physician assessments were not significantly different for midazolam (with or without narcotics) versus propofol except for slightly less patient satisfaction (RR 0.90, range 0.83-0.97) and more frequent memory (RR 3.00, range 1.25-7.21) with midazolam plus narcotics. Procedure times were similar, but sedation and recovery times were shorter with propofol than midazolam-based regimens. The authors concluded that moderate sedation provided a high level of physician and patient satisfaction and a low risk of serious adverse events with all currently available agents.

Singh et al, 2008 (2) performed a Cochrane systematic review comparing the relative effectiveness, patient acceptance and safety of propofol for colonoscopy, to traditional sedatives (narcotics and/or benzodiazepines). 20 RCTs were included. They found that recovery time, discharge time and patient satisfaction were in favour of propofol alone or in combination with other agents whereas there were no differences in procedure time, caecal intubation rate or complications. Authors concluded that Propofol for sedation during colonoscopy for generally healthy individuals can lead to faster recovery and discharge times, increased patient satisfaction without an increase in side-effects. Propofol is a reasonable option for sedation during colonoscopy for generally healthy individuals. Propofol may provide an advantage to endoscopy units, where the throughput of procedures is limited by the availability of recovery room resources. Faster turnover of patients through such endoscopy suites using propofol may help meet some of the increasing demands for endoscopy. Moreover higher patient satisfaction when propofol is used for sedation during colonoscopy may also lead to higher patient compliance with subsequent endoscopies.

Gasparovic et al, 2006 (3) analysed the respiratory effects of propofol on patients undergoing gastroscopy and colonoscopy. 1,104 patients were analysed, the results showed that propofol provided good sedation with excellent pain control and without serious adverse events

CONCLUSIONS

No RCTs comparing sedation with no sedation for colonoscopy were found by the searches we performed, although 3 studies were found comparing this in relation to upper endoscopy (assessed in the systematic review by McQuaid et al, 2008). The majority of the studies assessed different kinds of moderate sedation versus each other and they found that moderate sedation provides a high level of physician and patient satisfaction with low risk of serious adverse events. Propofol seems to be better than benzodiazepines or narcotics with regard to recovery, discharge time and patient satisfaction and is equivalent on procedure time, caecal intubation rate and adverse events (LEVEL OF EVIDENCE I).

Only one cohort study was found on deep sedation on 1,104 patients undergoing gastroscopy or colonoscopy. The results showed that propofol provided good sedation with excellent pain control and without serious adverse events (LEVEL OF EVIDENCE III).

UPDATE
SEARCH METHOD

Searches were conducted on MedLine and Embase for RCTs, systematic reviews and meta-analyses published in English between July 2007 and January 2009 because the searches of the review of Cochrane Database (Singh 2008 (2)) is update to June 2007.
Pubmed
The following free text searches produced 26 (included the reviews Singh H, 2008 (2) and McQuaid KR, 2008 (1)) results with 6 papers (1 review and 4 RCT) deemed relevant:
('colonoscopy AND sedation') OR ('colonoscopy AND hypnotic sedative agent') OR ('colonoscopy AND anesthesia') OR ('colonoscopy AND anesthetic') OR (colonoscopy AND premedication) OR
('colonoscopy AND midazolam') OR ('colonoscopy AND diazepam') OR ('colonoscopy AND meperidine')

OR ('colonoscopy AND fentanyl') OR ('colonoscopy AND propofol') OR ('colonoscopy AND diphenhydramine') OR ('colonoscopy AND promethazine') OR ('colonoscopy AND droperidol')

The review found (Lubarsky 2007 (4)) but the study was not considered because it is a narrative review without description of search strategy, inclusion criteria, and no. of included and excluded studies. Two RCT (Morrow JB 2000 (5), Radaelli F, 2003 (6)) included in this review and not evaluated in Singh H, 2008 (2) or McQuaid KR, 2008 (1) were included in our review.

Embase

Search terms:
('colonoscopy AND sedation') OR ('colonoscopy AND hypnotic sedative agent') OR ('colonoscopy AND anesthesia') OR ('colonoscopy AND anesthetic') OR (colonoscopy AND premedication) OR ('colonoscopy AND midazolam') OR ('colonoscopy AND diazepam') OR ('colonoscopy AND meperidine') OR ('colonoscopy AND fentanyl') OR ('colonoscopy AND propofol') OR ('colonoscopy AND diphenhydramine') OR ('colonoscopy AND promethazine') OR ('colonoscopy AND droperidol')

Limits: English language; Type of publication. Review, article; publication year: 2008-2009
The search terms identified 38 papers with 4 papers deemed relevant but included in the Pubmed search.

Moreover the primary studies on sedation for colonoscopy included in the McQuaid review (21) have been acquired in full text and data abstracted, because the review did not present separate results for studies on upper endoscopy and colonoscopy

RESULTS

Six randomised controlled trials were retrieved for this question.

Lazaraki 2007 (7) performed a randomised trial comparing the efficacy and safety of intravenous administration of fentanyl in titrated doses compared with intravenous administration of the well-known midazolam in titrated doses in 126 patients scheduled for ambulatory colonoscopy. Mean discomfort scores were 0.4 in the Fentanyl group and 1.0 in the Midazolam group (p = 0.002). Similarly, mean scores for pain and anus to cecum time were lower in the Fentanyl group than in the Midazolam group [2.59 vs. 4.43 (p = 0.002) and 8.7 vs. 12.9 min (p = 0.012), respectively]. No adverse events were reported in the Fentanyl group, while in the Midazolam group a decrease in oxygen saturation was noted in 23/60 (35%) patients. Mean recovery time was 5.6 min in the Fentanyl group and 16 min in the Midazolam group (p = 0.014).

Cohen LB 2008 (8) conducted a randomised, double-blind, multicentre trial to assess the efficacy and safety of fospropofol disodium in providing sedation in 127 patients undergoing colonoscopy who received different doses of fospropofol or midazolam. Fospropofol produced a significant dose-dependent increase in sedation success from 24% (2 mg/kg), 35% (5 mg/kg) and 69% (6.5 mg/kg) to 96% (8 mg/kg; P <0.001); sedation success in the midazolam group was 80.8%. Fospropofol produced also a significant dose-dependent increase in treatment success from 36% (2 mg/kg), 42% (5 mg/kg) and 81% (6.5 mg/kg) to 96% (8 mg/kg; P <0.001); treatment success in the midazolam group was 89%. There were no significant differences for time to discharge and patients satisfaction. Fospropofol and midazolam were well tolerated and there were no major treatment-emergent adverse events. Four patients receiving fospropofol experienced sedation-related AEs including mild hypotension [FP 5.0 (n = 1) and FP 6.5 (n = 1)] and hypoxaemia [FP 6.5 (n = 2); one classified as mild hypotension and one classified as moderate hypotension]. Of these four patients, one patient (FP 6.5 group) required airway assistance (verbal stimulation) for the treatment of hypoxaemia. One event (not described) led to discontinuation of the procedure in the midazolam group.

Mandel JE 2008 (9) performed a double-blind randomised controlled trial comparing the time to sedation and ambulation at equivalents levels of satisfaction in 50 patients undergoing elective colonoscopy who received midazolam/fentanyl or propofol/remifentanil administered via PCS.

Propofol/remifentanil patients were sedated and recovered significantly more rapidly than midazolam/ fentanyl patients (P <0.0001). Patient, nurse, and gastroenterologist perceptions were equivalent between the groups. Two patients in the propofol/remifentanil group required anesthesiologist intervention for arterial desaturation exceeding the primary safety end point.

Manolaraki MM 2008 (10), performed a randomised controlled trial to compare the safety and efficacy of remifentanil with those of the standard combination of midazolam and pethidine in 116 patients undergoing colonoscopy. Recovery was faster in remifentanil group (0 min) than in midazolam/pethidine group (56 ± 11.3 min) (P <0.001). There was a marked difference between the remifentanil and the midazolam/pethidine group with regard to the time of hospital discharge: 28.7 ± 4.3 and 148.9 ± 34 min, respectively (P <0.001). There was no statistical difference between groups for pain and patient comfort level. A combination of midazolam and pethidine had a greater affect on patient cardiorespiratory parameters. Author concluded that Remifentanil during colonoscopy provides sufficient pain relief with better hemodynamic stability, less respiratory depression, and significantly faster recovery and hospital discharge than moderate sedation with midazolam and pethidine.

Morrow JD, 2000 (5) performed a double blind randomised controlled trial comparing the safety and efficacy of titration, as outlined in practice guidelines, with a single, rapid bolus of sedatives in 101 patients undergoing colonoscopy. Titration required more physician time than did bolus (32.2 min vs 20.1 min, p <0.001) and was associated with an increased need for supplemental O2 (44% vs 14%, p =0.002). Mean tolerance scores were similar (titration 16.3 vs bolus 15.3, p=0.72). Authors concluded that bolus technique required less medication, yet provided equally acceptable levels of patient comfort and tolerance. Furthermore, bolus dosing caused less hypoxemia and saved significant endoscopist time. Based on this prospective evaluation, bolus dosing seems to be a superior technique for providing sedation and analgesia during colonoscopy

Radaelli F, 2003 (6) conduced a double blind randomised controlled trial comparing patient tolerance in 253 patients undergoing outpatient colonoscopy who received a single rapid intravenous bolus of midazolam and placebo or midazolam plus meperidine. Significantly more patients in midazolam alone group reported moderate or severe pain (28% vs. 9%; p <0.001), poor or unbearable tolerance (18% vs. 6%; p <0.01) and unwillingness to undergo colonoscopy again in the future (14% vs. 5%; p <0.05). By multivariate analysis, randomisation to the midazolam alone group and younger age were the only variables independently associated with the risk of reporting at least one of these outcomes. Recovery time, frequency of oxygen desaturation, and need for supplemental oxygen were not significantly different between the 2 groups. No serious adverse events occurred in both groups.

Primary studies on colonoscopy included in the review of McQuaid

Van Natta & Rex 2006 (11) performed an RCT To compare recovery time, patient satisfaction, and other end points with propofol alone titrated to deep sedation versus propofol combination therapy with opioids and/or benzodiazepines. 200 patients undergoing colonoscopy were randomised to the four groups: group P received propofol alone (n= 50), group F+ P received fentanyl plus propofol (n.50), the group M+ P received midazolam prior to propofol (n= 50) and the group F+M+ P received fentanyl plus midazolam prior to propofol (n= 50). Patients receiving propofol alone received higher doses of propofol and had deeper sedation scores compared with combination therapy (both *p* <0.001). Patients receiving combination regimens were discharged more quickly (median 13.0–14.7 *versus* 18.1 min) than those receiving propofol alone (*p* <0.01). There were no differences in vital signs or oxygen saturation among the study arms. There were no significant differences in pain or satisfaction among the study arms in the recovery area. At a follow-up phone call, patients receiving fentanyl and propofol remembered more of the procedure than those in the other regimens (*p* <0.005) and remembered more pain than those receiving propofol alone (*p* <0.02). There were no serious complications in any group. Authors concluded that their data suggest that propofol combination therapy can be successfully used with much lighter levels of sedation than propofol alone, without reduction in patient satisfaction, with no reduction in time to full recovery or discharge, and with minimal loss of efficiency associated with time to initiate the procedure.

Tu 2006 (12) performed an RCT to determine if the addition of diphenhydramine to midazolam and meperidine before colonoscopy could improve sedation and could decrease the usage of benzodiazepines and opiates without compromising the success of colonoscopy, procedure length, or recovery time. 258 patients undergoing colonoscopy were randomised to receive diphenhydramine (n= 130) or placebo (0.9% sodium chloride IV) (n= 128). There was a 10.1% reduction in meperidine usage and 13.7% reduction in midazolam usage in favor of the diphenhydramine group. The mean evaluation scores as judged by the faculty, the fellows, and the nurses were statistically significant in favour of the diphenhydramine group. In addition, patient scores for overall sedation and pain level favoured the group that received diphenhydramine. No serious adverse events were reported in both groups. Authors concluded that the addition of diphenhydramine to routine sedation significantly improved the overall sedation scores. Recollection of the procedure and pain scores as reported by the patient, were significantly better in the diphenhydramine group. Their data strongly suggest that diphenhydramine can be used effectively as an adjunct, providing overall superior sedation when compared with the use of traditional sedatives alone.

Arici 2003 (13) realized an RCT to compare the effectiveness of remifentanil/midazolam, and tramadol/midazolam for IV sedation and analgesia during colonoscopy. 36 patients undergoing colonoscopy were randomised to receive midazolam plus remifentalin (group R=18) or midazolam plus tramadol (group T=18). Hemodynamic parameters, heart rate, patient satisfaction were comparable between groups. The level of sedation was higher in the remifentanil/midazolam group and the pain score was lower. No serious complications were reported. Authors concluded that sedoanalgesia with midazolam/remifentanil may be an alternative to sedoanalgesia with midazolam/tramadol for colonoscopy.

Zakko 1999 (14) performd an RCT to determine clinically equivalent doses for midazolam and diazepam in human subjects; (2) to determine the effect of age and gender on the sedative dose of these medications; and (3) to determine the effect of these clinically equivalent doses of midazolam and diazepam on resting ventilation and oxygenation. 100 subjects were randomised in two groups of 50 patients receiving meperidine followed by midazolam (group M: 23 men and 26 women; mean age 59 ± 2) or diazepam. The study found that Midazolam was 3.4 times more potent than diazepam. The duration of oxygen desaturation emphasizes the importance of monitoring SpO2 until ventilation and oxygenation have recovered. Although the degree of hypoxemia was comparable, midazolam led to higher end-tidal carbon dioxide tensions. Adverse events are not reported.

Ginsberg 1992 (15) performed an RCT to evaluate the efficacy of the currently recommended low doses of midazolam for conscious sedation compared with diazepam for colonoscopy. 53 patients undergoing colonoscopy were randomised to receive diazepam plus meperidine (group A=24) or midazolam plus meperidine (group B=29) . No significant differences for recovery time and procedure time between the groups were found. The low initial and incremental doses of midazolam compared favorably with diazepam in all efficacy parameters studied and exceeded diazepam in post-procedure amnesia scores (p = 0.01). No results were reported on adverse effects.

Di Palma 1995 (16) performed an RCT To determine whether the narcotic alfentanil, alone or in combination with midazolam has advantages over the traditional meperidine and midazolam regimen for conscious sedation. 35 patients undergoing colonoscopy were randomised to receive midazolam plus alfentanil (group A=11) or midazolam plus meperidine (group B=11) or placebo and alfentanil (group C=13). No differences as assessed by patient and colonoscopist for tolerance and discomfort, procedure ease, recovery time, complications, electrocardiogram, and blood pressure were found. Authors concluded that alfentanil, with or without a sedative, has no advantage over the commonly used meperidine and midazolam regimen.

CONCLUSIONS

No RCTs were found during the update search comparing sedation with no sedation for colonoscopy. The majority of retrieved studies compared different types of moderate sedation versus each other. Propofol or opiates seem to be better than benzodiazepines on discharge time, patient safety and

satisfaction. No serious adverse effects were reported for all treatment groups in all retrieved studies (LEVEL OF EVIDENCE I).

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5.7.2 Evidence tables

Author, publication year	Study Objective Study Design	Intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
McQuaid 2008	To compare efficacy, safety, and efficiency of agents used for moderate sedation in upper endoscopy or colonoscopy. Systematic review of randomised trials of moderate sedation that compared 2 active regimens or 1 active regimen with placebo or no sedation. SEARCH	Experimental intervention: moderate sedation Control intervention: different type of moderate sedation, placebo, no sedation	Thirty-six studies (N = 3918 patients) which included unselected adults undergoing EGD or colonoscopy . 12 studies on colonoscopy 21 studies on upper endoscopy 3 studies on both procedures 75 treatment arms: no sedation (3), diazepam alone (10), midazolam alone (16), propofol alone (8),narcotic alone (2), diazepam plus narcotics (4), midazolam plus narcotics (22), propofol plus narcotics (4), propofol plus midazolam (3), propofol plus midazolam plus narcotics (1), diphenhydramine plus midazolam plus narcotic (1), and droperidol plus midazolam plus narcotic (1).	sedation-related outcomes: patient monitoring/complications (eg, hemodynamic monitoring, hemoglobin oxygen saturation, end-tidal carbon dioxide, need for reversal agents, adverse events), procedure- or efficiency-related outcomes (eg, sedation time, procedure time, recovery time), patient assessment of procedure (eg, satisfaction, pain or discomfort assessment, memory/recollection of procedure, willingness to repeat examination), physician assessment of procedure (eg, satisfaction with sedation, level of sedation, assessment of patient cooperation or examination quality).	Comparison have been done considering studies in upper endoscopy and colonoscopy altogether. **Sedation versus no sedation** No studies were found in colonoscopy for this comparison Patient: satisfaction 2 studies RR 2.29 (1.16-4.53) Patient willingness to repeat examination 2 studies RR 1.25 (1.13-1.38) **Midazolam versus diazepam** No studies were found in colonoscopy for this comparison patient cooperation 3 studies 1.20 (0.75-1.91) Patient satisfaction 2 studies RR 1.18 (1.07-1.29) Patient willingness to repeat 4 studies RR 1.08 (1.04-1.13) Patient memory of examination 5 studies RR 0.57 (0.50-0.65) Patient O - mild pain 2 studies RR 0.44 (0.03-6.53) **Midazolam plus narcotic versus diazepam plus narcotic** Hypoxemia 2 studies RR 0.97 (0.41-2.31) Need for supplemental oxygen 2 studies RR 0.87 (0.47-1.63) Physician: satisfaction with examination 2 studies RR 1.06 (0.96-1.18) Patient O - mild pain 3 studies RR 0.91 (0.61-1.37)	**I** The marked variability in study design, methodologic quality, regimens tested, and outcomes assessed in the studies included limited the ability to define an ''optimal'' moderate sedation regimen. Pooling results from multiple studies was particularly problematic because of differences among studies in the centers, patient populations, geographic locations, physician practices, endoscopic techniques, methods and levels of sedation, and measurement of sedation end points. In summary, this systematic review of RCTs confirms that sedation for routine EGD and colonoscopy provides a high level of physician and patient satisfaction and a low risk of clinically significant adverse events with all currently available agents. Meta-analyses of trials comparing propofol versus midazolam found no significant differences in most important clinical

Author, publication year	Study Objective Study Design	Intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
					Midazolam versus propofol Hypoxemia 2 studies RR1.11 (0.71-1.74) Patient: satisfaction 2 studies RR 0.99 (0.86-1.14) Patient willingness to repeat 2 studies RR 1.11 (0.98-1.25) Patient memory of examination 3 studies RR 0.63 (0.35-1.19) **Midazolam plus narcotic versus propofol** Hypoxemia 3 studies RR 0.82 (0.22-2.98) Bradycardia 3 studies RR 1.00 (0.30-3.36) Hypotension 3 studies RR 1.28 (0.51-3.26) Physician satisfaction with examination 2 studies RR 0.84 (0.68-1.04) Patient satisfaction 2 studies RR 0.90 (0.83-0.97) Patient O - mild pain 2 studies RR 0.90 (0.37-131.3) Patient memory of examination 2 studies RR 3.00 (1.25-7.21)	outcomes for EGD but a higher proportion of patient satisfaction for colonoscopy with propofol sedation. Recovery times for both EGD and colonoscopy were shorter with propofol than with midazolam with or without narcotics, potentially increasing the number of cases that can be performed in an endoscopy unit. Controlled trials are needed to assess the role of lower doses of propofol in combination with midazolam or narcotics compared with propofol alone or benzodiazepines plus narcotics.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	Medline, Embase
	Date restriction	Up to January 2007
	any restriction	Only studies published in English
Selection	Inclusion and exclusion criteria	randomised trials of moderate sedation that compared 2 active regimens or 1 active regimen with placebo or no sedation.
Validity assessment	Criteria and process used	Methodological quality assessed using validated criteria
Data abstraction	Process used	Data abstraction perfromed by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	RR with 95% CI; statistical heterogeneity assessed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study Objective Study Design	Study Participants	Intervention	Outcomes	Results	Conclusion Level of evidence
Gašparović et al. 2006	To analyse the hemodynamic and respiratory effects of propofol on patients undergoing gastroscopy and colonoscopy. Prospective study Conducted over a period of three years, Croatia	1,104 patients (639 women and 465 men) admitted for colonoscopy (521 patients), gastroscopy (310 patients) or both procedures (273 patients).	Gastroscopy or colonoscopy with sedation using propofol bolus (0.5-1.5 mg/kg)..	Arterial blood pressure every three minutes Heart rate and Oxygen saturation continuously by pulse oximetry Pain score Recovery time complication	propofol in dosages of 0.5-1.5 mg/kg decreased the systolic blood pressure from 149.8 to 112.2 mmHg, diastolic blood pressure from 80.6 to 68.4 mmHg and heart rate from 88.4 to 81.3 beats/min. Hypotension, defined as a blood pressure bellow 60 mmHg, was recorded in 5 patients (0.5%) Oxygen saturation also decreased during the procedure from 96.5% to 94.4% (P <0.001). Oxygen saturation of less than 90% was documented in 27 patients (2.4%). Seven of them were in ASA class III with cardiopulmonary disease, 14 patients with hypertension and obesity and 6 patients were older than 80 years. All hypoxemic episodes occurred in patients undergoing an upper GI examination. No episodes of apnea occurred and mechanical ventilation was not employed in any of our patients. The hypoxemia proved to be transient in all the patients.	**III** Our results showed that propofol provided good sedation with excellent pain control, a short recovery time and no significant hemodynamic side effects if carefully titrated. All the patients (and especially ASA III group) require monitoring and care of an anesthesiologist.

Quality assessment: cohort representative of patients normally undergoing endoscopic procedures. No controls. Outcomes described.

Author, publication year	Study Objective Study Design	intervention	Included studies	outcomes	Results	Conclusion Level of evidence
Singh 2008	To compare the relative effectiveness, patient acceptance and safety of propofol for colonoscopy, to traditional sedatives Cochrane Systematic review of randomised comparing use of propofol and traditional agents. SEARCH Medline, Cancerlit, EMBASE, CINAHL, LILACS, Biological Abstracts, Web of Science and the Cochrane Library. January 1980 - June 2007; conference proceeding 1990 - June 2007	Experimental intervention: propofol Control intervention: traditional agents (benzodiazepines, narcotics). The intended level of sedation in most studies was determined by the patient tolerance of the procedure	20 studies which included unselected adults colonoscopy . 1.Comparison : propofol as single agent vs traditional 2. Propofol + traditional vs traditional 3. All studies toghether	Technical performance of colonoscopy: caecal intubation rate, time required for performing the procedure, post procedure recovery and discharge time and sedation level Patient satisfaction and pain control Complication rates: cardio respiratory events (hypoxia, apnea, hypoxia requiring intervention, hypotension, arrhythmias), colonic perforations and hospital admission rate after procedure (when procedure performed in ambulatory care setting) and death.	Recovery time: all studies WMD -14.2 minutes (95% CI -17.6-10.8) shorter with propofol, with no significant heterogeneity (p=0.41). Discharge times SMD -0.76 (95% CI -1.00-0.56), implying faster discharge with use of propofol as a single agent or in combination with another agent, with borderline heterogeneity (p=0.10). patient satisfaction :OR for dissatisfaction 0.35,(95% CI 0.23, 0.53) in favour of propofol. procedure time, caecal intubation rate or complications: no difference. There was no difference in pain control with non- patient controlled sedation (PCS) use of propofol as compared to the traditional agents (OR 0.90; 95% CI 0.58, 1.39). Although there was higher patient satisfaction (OR for dissatisfaction 0.42, 95% CI 0.20, 0.89), the pain control was inferior with use of PCS use of propofol as compared to the use of traditional agents (OR 3.09; 95% CI 2.15, 4.46).	I Propofol for sedation during colonoscopy for generally healthy individuals can lead to faster recovery and discharge times, increased patient satisfaction without an increase in side-effects. Propofol is a reasonable option for sedation during colonoscopy for generally healthy individuals. Propofol may provide an advantage to endoscopy units, where the throughput of procedures is limited by the availability of recovery room resources. Faster turnover of patients through such endoscopy suites using propofol may help meet some of the increasing demands for endoscopy. Moreover higher patient satisfaction when propofol is used for sedation during colonoscopy may also lead to higher patient compliance with subsequent endoscopies. Differences in patient outcomes depend upon not only on the choice of the sedative agent, but also on how the particular sedative agent is used

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	Medline, cancerlit, embase, cinahl, lilacs, biological abstracts, web of science and the cochrane library. Conference proceedings
	Date restriction	Up to June 2007
	any restriction	No restriction
Selection	Inclusion and exclusion criteria	randomised trails comparing use of propofol and traditional agents
Validity assessment	Criteria and process used	Methodological quality assessed using validated criteria
Data abstraction	Process used	Data abstraction performed by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	OR with 95% CI for dichotomous outcomes; WMD or SMD with 95%CI for continuous outcomes; statistical heterogeneity assessed
Results Trial flows	Trial flow and reason for exclusion	Yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Yes

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Lazaraki G, 2007	The aim of this study was to evaluate the efficacy and safety of intravenous administration of fentanyl in titrated doses compared with intravenous administration of the well-known midazolam in titrated doses. Randomised controlled trial Greece	Number of eligible patients: 149 Number of patients enrolled: 126 (14 excluded for abdominal hernia, 3 for poor preparation and 2 for mild cognitive impairment) 126 patients undergoing colonoscopy were randomised to receive fentanyl (group F=31 men and 35 women; mean age 61.5) or midazolam (group M= 27 men and 33 women; mean age 63.2) No difference between groups for age, BMI and clinical data.	Colonoscopy with sedation using: F: 25 mcg fentanyl and titrated up to 50 mcg (n=66) or M: 2mg midazolam and titrated up to 5 mg (n=60)	Complications, recovery time, patient satisfaction, pain and discomfort, procedure time	Mean recovery time (min) F 5.6 vs M 16 (p=0.014) No adverse events in F group. A decrease in oxygen saturation in 23/60 (35%) patients of M group Mean discomfort score (0-4) F 0.4 vs M 1.0 (p=0.002) Mean pain score (0-10) F 2.59 vs M 4.43 (p=0.002) Mean Dose Group F= 36 mcg Group M= 4.6 mg Mean time to cecum (min) F 8.7 vs M 12.9 (p=0.012) Memory of procedure (%) F 100 vs M 53 (p=0.001)	II The application of fentanyl in low incremental bolus doses for colonoscopy may yield even better levels of safety compared with the conventional administration of midazolam and, moreover, this results in a higher level of patient satisfaction and a shorter recovery period.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: unclear; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Cohen L.B., 2008	To assess the efficacy and safety of fospropofol disodium in providing sedation in patients undergoing colonoscopy. Randomised, double-blind, multicentre trial New York, USA	127 patients undergoing colonoscopy were randomised to receive 2 mg∕kg of fospropofol (group FP 2.0: 12 men 13 women; mean age 54.6± 10.4) or 5 mg∕kg of fospropofol (group FP 5.0: 14 men 12 women; mean age 55.5± 11.1) or 6.5 mg∕kg of fospropofol (group FP 6.5: 11 men 15 women; mean age 54.2±15.2) or 8.0 mg∕kg of fospropofol (group FP 8.0: 11 men 13 women; mean age 53.4±14.5) or midazolam (group MD: 10 men 16 women; mean age 53.9±11.9). Pre-treatment with fentanyl for all patients No difference among groups for age, race, gender, ASA status, weight.	Colonoscopy with sedation using: FP 2.0: fentanyl (50 μg) followed by fospropofol (2 mg∕kg) (n=25) or FP 5.0: fentanyl (50 μg) followed by fospropofol (5 mg∕kg) (n=26) or FP 6.5: fentanyl (50 μg) followed by fospropofol (6.5 mg∕kg) (n=26) or FP 8.0: fentanyl (50 μg) followed by fospropofol (8.0 mg∕kg) (n=24) or MD: fentanyl (50 μg) followed by midazolam (0.02 mg∕kg) (n=26)	<u>Sedation success</u>, defined as : three consecutive MOAA∕S scores of ≤4 after administration of sedative medication, (ii) completion of procedure without use of alternative sedative medications and (iii) no requirement for either manual or mechanical ventilation. depth of sedation . (MOAA/S), memory retention, patient and doctor satisfaction, safety	<u>Sedation success (%)</u> Dose-dependent across fospropofol treatment groups. FP2.0 24% FP5.0 34.6% FP6.5 69.2% FP8.0 95.8% MD 80.8% *(p<0.001)* <u>Treatment success (%)</u> Dose-dependent increase in treatment success across the fospropofol dosing groups. FP2 36% FP5. 42% FP6.5 81% FP8. 96% MD 89% (p<0.001) <u>Mean time discharge time (min)</u> FP2.0 15.0 ±19.6 FP5.0 7.8±10.5 FP6.5 9.1±7.8 FP8.0 14.2±13.4 MD 10.2±14.1 *(p ns)* <u>Depth of sedation</u> The majority of patients in each groups had mean MOAA/S scores ranging from 2 to 4. MOAA/S= 0 or 1 6 patients of FP 8.0 2 patients of FP 2.0 1 patient of FP 5.0 1 patient of FP 5.0 <u>Mean Memory retention (%)</u> No significant differences	**II** The results of this study demonstrate that administration of fospropofol disodium results in a level of sedation that is safe and effective for patients undergoing colonoscopy. On the basis of this study, we believe that the 6.5 mg∕kg dose of fospropofol provides the ideal balance of efficacy and safety. This study also demonstrates that the safety profile of fospropofol compares favourably with that of other sedatives such as midazolam. If the results of this study are supported by the findings of a phase 3 trial, fospropofol could provide a useful alternative to the agents currently in use for endoscopic sedation.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					Safety No serious adverse event or deaths during the study. One event led to discontinuation of the procedure (MD). 2 episode of mild hypotension (FP 5.0=1 and FP 6.5=1). 2 episode of hypoxaemia (FP 6.5) and 1 of these required airway assistance. <u>Patient Overall satisfaction rated as high (9-10%)</u> FP2.0 72.0% FP5.0 84.0% FP6.5 92.3% FP8.0 79.2% M 69.2% P: NS <u>Doctor Overall satisfaction rated as high (9-10%)</u> FP2.0 8.0% FP5.0 11.5% FP6.5 26.9% FP8.0 50.0% *(p=0.0028)* M 11.5%	

Quality assessment: allocation concealment: adequate; blindness of provider: yes; blindness of patients: yes; blindness of clinical staff: yes; blindness of outcome assessor: yes. None lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Mandel 2008	To determine whether the combination of propofol and remifentanil using PCS (patient controlled sedation) could significantly reduce the time to sedation and ambulation without assistance when compared with midazolam and fentanyl at equivalent levels of patient, nurse, and gastroenterologist satisfaction. Randomised controlled trial (double blind). Philadelphia, Pennsylvania.	50 patients (1 patient excluded for noncompliance with bowel preparation) undergoing colonoscopy were randomised to receive midazolam plus fentanyl (group MF=24; mean age 57.7 ± 10.8) or propofol plus remifentanil (group PR= 25; mean age 60.5 ± 9.6) No difference between groups for age, BMI, gender, and number of ASA III patients.	Colonoscopy with sedation administered via PCS using: MF: midazolam (1mg/mL), fentanyl (50 µg/mL), and 5 mL of saline (n=24) PR: remifentanil (1 mg) in 2.5 mL of propofol (10 mg/mL) and adding 1 mL of this mixture to 39 mL of propofol. (n=25).	Time intervals for sedation and recovery, perceptions by patient, nurse, and gastroenterologist, and need for anaesthesiologist intervention	Mean Time to sedation (min) MF 7.6± 3.6 vs PR 3.4 ±1.3 (p<0.0001) Time to ambulation (min) MF 36.4±5.3 vs PR 9.2± 4.0 (p<0.0001) Recovery room time MF 32± 25 vs 4.9±4.3 (p<0.0001) Age, gender, height, weight, BMI, and gastroenterologist were not confounders for time to sedation, time to ambulation and recovery room time. Procedure room time No significantly different between groups. Satisfaction of patient, nurse, and gastroenterologist No correlation (orderered logit regression) between ratings and group, gender, age, height, weight, or BMI. Two patients (group PR) required anesthesiologist intervention for arterial desaturation exceeding the primary safety end point. No technical complications of colonoscopy. All patients completed colonoscopy without non-PCS sedation.	**II** Group PR patients were sedated and recovered significantly more rapidly than did group MF (*P* _ 0.0001). In the group PR, recovery room time was actually shorter than procedure room time. Patient, nurse, and gastroenterologist perceptions were equivalent between the groups. Two patients in group PR required anesthesiologist intervention for arterial desaturation exceeding the primary safety end point. PCS with propofol/remifentanil yields superior facility throughout compared with midazolam/fentanyl when used in an appropriate care setting. We cannot recommend this form of sedation to those not prepared to administer resuscitative measures promptly, and do not suggest that the methods used in this study are standard clinical practice. The extent to which PCS with anesthesiologist rescue can form the basis of a safe, cost-effective alternative to a two-tiered system of conscious sedation by nurses and deep sedation in a monitored anesthesia care model will require further study.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: yes; blindness of gastroenterologist and nurse: yes; blindness of anesthesiologist: yes before allocation, no after allocation to intervene for adverse events; blindness of outcome assessor: yes; lost at follow up: one patient was excluded for noncompliance with bowel preparation.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Manolaraki 2008	To compare the safety and efficacy of remifentanil during colonoscopy with those of the standard combination of midazolam and pethidine. Prospective, randomised controlled trial Greece	116 patients undergoing colonoscopy were randomised to receive intravenous midazolam and pethidine (group A=24 men and 22 women; mean age 60.2±11.5) or intravenous remifentanil (group B= 33 men and 27 women; mean age 60.3±15.9) No difference between groups for age, gender, ASA grade, weight, height.	Colonoscopy with sedation using: A: 50 mg pethidine followed by midazolam. In case of no tolerance of procedure, a supplemental dose of pethidine (25–75 mg) and additional midazolam, up to a cumulative dose of 0.1 mg kg^{-1} body weight (n=56) or B: 1 µg kg–1 remifentanil over 60 s followed by continuous infusion at an initial rate of 0.05 µg kg^{-1} min^{-1} (n=60)	Patient comfort, safety, recovery (APRS-modified Adrete scores), discharge (MPADS scores).	No difference between groups for <u>duration of CT.</u> <u>Number of drop in O_2 saturation</u> A 18% *vs* B 1.6% *(p<0.005)* <u>Drop in rate of respiration</u> A 28.5%*vs* B 0% *(p<0.001)* <u>Drop in blood pressure</u> A 46.4% *vs* B 1.6% *(p<0.001)* No cardiopulmonary <u>complications</u> in either group<u>.</u> <u>Mean sedation score</u> Mean level of sedation was significantly higher in group A than in group B (A 2.8±0.4 vs B 1.4±0.4 *(p<0.001)*. During remifentanil administration all patients were mildly sedated, gave a lethargic. response to verbal commands, and had mild ptosis of the eyes. Although the target level of sedation in group A was moderate sedation, most of those patients were moved to deep sedation during the procedure. <u>Pain (VAS)</u> A 0.8±1.5 vs B 1.15±1.34 *(p ns)* <u>Mean patient comfort level (1-4 scale)</u> A 3.7±0.5 vs B 3.7±0.5 *(p ns)* <u>Mean endoscopist comfort level (1-4 scale)</u> A 3.6±0.5 vs B 3.6±0.5 *(p ns)* <u>Recovery (APRS of 10-min)</u> A 56±11.3 vs B 0±0 *(p<0.001)*	**II** Remifentanil during colonoscopy provides sufficient pain relief with better hemodynamic stability, less respiratory depression, and significantly faster recovery and hospital discharge than moderate sedation with midazolam and pethidine. Our results suggest that use of remifentanil as a single agent during colonoscopy is associated with faster patient recovery, and thus a shorter stay in hospital, than synergistic sedation with midazolam and pethidine, without affecting patient safety or satisfaction. Our results also reinforce the hypothesis that if pain were relieved adequately during colonoscopy sedation would no longer be

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					<u>Discharge (MPADS of 10-min)</u> A 148.9±34 vs B 28.7±4.3 *(p<0.001)* From the endoscopist's point of view both groups cooperated adequately with no statistical differences between the two study groups Median discharge time for group B was 5.5 times less than for group A. No significant differences between post-procedural adverse events in the two groups. Nausea and vomiting for 5 patients (A=3 B=2) No complications or deaths associated with the colonoscopy were recorded during the 30-day evaluation.	required. Patients receiving remifentanil during colonoscopy should, however, be aware, and accept that, they will probably be conscious during the examination. The safety profile of remifentanil was comparable to that of synergistic sedation. These results should be confirmed in larger studies.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of clinical staff: no; blindness of outcome assessor: no. None lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Morrow 2000	To compare the safety and efficacy of titration, as outlined in practice guidelines, with a single, rapid bolus of sedatives before colonoscopy. Prospective, randomised controlled trial (double blind). Cleveland, Ohio USA	Number of eligible patients: 105 Number of patients enrolled: 101 101 patients undergoing colonoscopy were randomised to receive a single, rapid bolus of meperidine and midazolam (group B=24 men and 25 women; mean age 47.9) or to a titration of doses every 3 min until predefined levels of somnolence (group T= 26 men and 26 women; mean age 49.7) No significant difference between groups for age, gender, anxiety, current smoker, prior hysterectomy, prior abdominal surgery, prior colonoscopy/ sigmoidoscopy.	Colonoscopy with sedation using: B: a single, rapid injection of meperidine and midazolam (the dose coming from a nomogram based on age and weight) (n=49) T: initial intravenous dose of 25 mg of meperidine and 1mg of midazolam followed by further doses (25 mg meperidine to 1 mg midazolam, or 12.5 mg meperidine to 0.5 mg of midazolam) titrated every 3 min until predefined endpoints of titration or significant changes in cardiorespiratory parameters (n=52).	Sedation time, procedure time, depth of sedation, discharge, patient pain and tolerance (VAS), endoscopist assessment, adverse events	A multiple regression analysis found gender, anxiety, and insertion time to the cecum to be the clinical variables significantly related to patient pain and tolerance. Modelbased mean scores for pain and tolerance were determined, adjusting for these significant factors <u>Tolerance scores and Pain scores</u> No significant differences between group B and T for either mean tolerance or mean pain scores. <u>Endoscopist pain and tolerance</u> No significant differences in mean scores between group B and T. <u>Recovery time</u> No significant difference <u>Sedation time</u> B 3.0± 0.1 vs T 11.0± 1.1 ($p<0.001$) <u>Procedure time</u> B 17.1± 1.1 vs T 21.2± 2.0 ($p=0.09$) <u>Total physician time</u> B 20.1± 2.0 vs T 32.2± 2.0 ($p<0.001$) There was a significant difference in initial sedation time ($p<0.001$), but not procedure time (p: 0.09). Likewise, there was a significant difference in total physician time (p, 0.001), with the titration technique requiring an additional 12.1 min/case. <u>Total dose of meperidine</u> B 66.5± 1.5 vs T 82.9±3.2 ($p<0.001$) <u>Total dose of midazolam</u> B 2.7 ± 0.1 vs T 3.3 ±0.1 ($p<0.001$)	II Bolus technique required less medication, yet provided equally acceptable levels of patient comfort and tolerance. Furthermore, bolus dosing caused less hypoxemia and saved significant endoscopist time. Based on this prospective evaluation, we believe that bolus dosing is a superior technique for providing sedation and analgesia during colonoscopy.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					Somnolence score<3 B 20 (41%) *vs* T 39 (75%) *(p=0.001)* When compared to the bolus group, patients in the titration group received significantly higher doses of medication (p, 0.001) and were judged to be more deeply sedated (p, 0.001). Number of Adverse events SaO_2<90% B 15 *vs* T 34 (*p<0.001*) Required supp. O_2 B 7 *vs* T 23 (*p<0.001*) Patients in the titration group were more likely to have either a single episode of SaO2 ,90% (p, 0.001) or to require supplemental oxygen for sustained desaturation (p, 0.001). Other events such as hypotension, tachycardia, bradycardia, and need for reversal agents were rare in both groups. No serious adverse events occurred in either study group.	

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: yes; blindness of clinicall staff: yes; blindness of outcome assessor: yes; lost at follow up: 1 for incomplete CT.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Radaelli 2003	To determine whether a single bolus of meperidine in addition to midazolam improves patient tolerance during colonoscopy. Prospective, randomised controlled trial (double blind). Como, Italy	Number of eligible patients: 500 Number of patients enrolled: 253 (the other excluded for exclusion criteria) 253 patients undergoing colonoscopy were randomised to receive a 2 rapid bolus injections of midazolam and placebo (group A=49 men and 76 women; mean age 58.9±14.1) or midazolam plus meperidine (group B= 53 men and 75 women; mean age 57.4±13.2) No significant difference between groups for age, gender, anxiety, current smoker, use of antispasmodic drugs.	Colonoscopy with sedation using: A: 2 rapid bolus injections of placebo and 5 mg of midazolam(n= 125) B: 50 mg meperidine followed by 5 mg of midazolam (n=128).	Adverse events, discharge, endoscopist assessments, assessment of tolerance, procedure time, recovery time	Mean time to cecum (min) A 9.3± 7.3 *vs* B 10± 9.4 *(p ns)* Mean total procedure time (min) A 18.8± 12.2 *vs* B 19.2± 13.8 *(p ns)* Adverse events $SaO_2 < 90\%$ A 11% *vs B* 16% (p=0.28) Required supplemental O_2 A 5% *vs* 9% (p=0.34) Reversal agent given A 1% *vs* 1% (p=0.99) (<60 min) Recovery time A 11% vs B 15% (p=0.35) Patient poor tolerance (4 point scale) A 18% *vs B* 6% (p=0.006) Patient moderate/severe pain (4 point scale) A 28% *vs B* 9% (p<0.001) Poor tolerance as assessed endoscopist (3 point scale) A 27% *vs* B12% (p=0.002) Multivariate analysis indicated that young age (OR=0.96 p=0.003) and randomisation to midazolam alone (OR=3.88 p=0.000)were the only independent factors positively related to the risk of reporting at least one of the following outcomes: moderate/severe pain, poor/unbearable tolerance, more discomfort than expected, or unwillingness to repeat the procedure; a statistically non significant trend was also found for female gender age (OR=1.95 p=0.088)and previous abdominal surgery age (OR=2.21 p=0.056).	**II** Midazolam and meperidine, given as single boluses to patients at low risk of cardiopulmonary complications, have an additive effect on patient tolerance for colonoscopy without significantly increasing the risk for cardiorespiratory complications or prolonging recovery time. This result endorses the current widespread use of this combination of medications for sedation of patients about to undergo colonoscopy.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: yes, blindness of endoscopists and recovery room personnel: yes, blindness of outcome assessor: yes; None lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Van Natta & Rex 2006	To compare recovery time, patient satisfaction, and other end points with propofol alone titrated to deep sedation versus propofol combination therapy with opioids and/or benzodiazepines. Randomised controlled trial Indianapolis (Indiana) USA	Number of eligible patients: 213 Number of patients enrolled: 200 (11 excluded because not consent, 1 because poor preparation, 1 because subcutaneous initial dose, 1 excluded prior to initiation of the CT) 200 patients undergoing colonoscopy were randomised to the four group: group P received propofol alone, group F+ P received fentanyl plus propofol , the group M+ P received midazolam prior to propofol and the group F+M+ P received fentanyl plus midazolam prior to propofol No difference among the group for age, race, gender and procedure indication.	Colonoscopy with sedation using P: propofol alone (n=50) F+P: fentanyl (50 µg) plus propofol (n=50) M+P: midazolam (1 mg)prior to propofol (n=50) F+M+ P: fentanyl (50 µg) plus midazolam (1 mg) prior to propofol (n=50).	Sedation score, propofol dosing, vital sign, oxygen saturations, pain, discharge and patient satisfaction in recovery	<u>Mean Propofol Dosing (mg)</u> P 215.0 *vs* F+P 140.0 *(p <0.0001)* P 215.0 *vs* M+P 125 *(p <0.0001)* P 215.0 *vs* F+M+P 82.5 *(p <0.0001)* <u>Mean sedation score(MOAA/S[6])</u> P 0.9 ± 1.1 *vs* F+P 3.9 ± 0.6 *(p <0.0001)* P 0.9 ± 1.1 *vs* M+P 3.2 ± 1.0*(p <0.0001)* P 0.9 ± 1.1 *vs* F+M+P 3.5 ± 0.7 *(p <0.0001)* <u>Vital sign</u> No statistical differences in vital signs or oxygen saturations among the group. <u>Discharge</u> (median-min) P 18.1 *vs* F+P 13.9 *(p <0.01)* P 18.1 *vs* M+P 13.9 *(p <0.01)* P 18.1 *vs* F+M+P 14.7 *(p <0.01)* <u>Patient satisfaction</u> No statistical differences in satisfaction scores among the group. <u>Pain</u> In the recovery room (VAS): P 0.4 ± 2.0 vs F+P 7.5 ± 14.6 (p<0.03) P 0.4 ± 2.0 vs F+M+P 1.6 ± 4.2 (p<0.03) P 0.4 ± 2.0 vs M+P 5.0 ± 16.7 (p=0.06) At a follow-up phone call: Patients of group F+P remembered more pain than those of group P (p <0.02). <u>Complications</u> No patient required assisted ventilation or treatment of hypotension or bradycardia. There was no difference among the	II Our data suggest that propofol combination therapy can be successfully used with much lighter levels of sedation than propofol alone, without reduction in patient satisfaction, with no reduction in time to full recovery or discharge, and with minimal loss of efficiency associated with time to initiate the procedure.

[6] Modified Observer's Assessment of Alertness/Sedation (MOAA/S).

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					groups in the lowest systolic blood pressure recorded, lowest diastolic blood pressure, lowest heart rate, or lowest oxygen saturation	

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: yes; blindness of clinical staff: no; blindness of outcome assessor: a) yes for assistant measuring MOAA/S and discharge time b) no for endoscopists and nurses administrating sedation; 1 patient lost at follow-up questionnaire: unclear in which group.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Tu R.H, 2006	To determine if the addition of diphenhy-dramine to midazolam and meperidine before colonoscopy could improve sedation and could decrease the usage of benzo-diazepines and opiates without compromising the success of colonoscopy, procedure length, or recovery time. Prospective, randomised, double-blind, placebo-controlled trial. Sacramento, California, USA	Number of eligible patients: 270 Number of patients enrolled: 258 (9 excluded because poor preparation, 2 because incompleteness of CT, 1 because colitis) 258 patients undergoing colonoscopy were randomised to receive diphenhy-dramine (group D: 61 men and 69 women; mean age 55.7 ± 11.5) or placebo (0.9%sodium chloride IV) (group P: 67 men and 61 women; mean age 53.4 ± 11.8). No significant difference between the group for age, gender, BMI, alcohol use, incomplete procedure.	Colonoscopy with sedation using : D: diphenhy-dramine (50 mg followed by meperidine in 25 mg increments and midazolam in 1 mg)(n=130) or P: placebo (50 mg followed by meperidine in 25 mg increments and midazolam in 1 mg) (n=128).	Sedation score, pain, medication dosages, cost of sedation, duration of CT and recovery, complications.	Mean sedation score (10 point scale) by staff D 9.04±1.32 vs P 8.30±2.04 ($p<0.001$) No difference in the adequacy of sedation between the group D and P as judged by the staff. Mean sedation score (10 point scale) by patient D 9.45±1.32 vs P 9.04±1.73 ($p=0.017$) Patient pain (10 point scale) D 1.74±1.62 vs P 2.34±2.3 ($p=0.008$) Patient preference For next colonoscopy, a significantly larger number of patients in the group P requested more sedation($p=0.003$) Patient recollection (10 point scale) D 2.64±2.7 vs P 3.68±3.32 ($p=0.003$) Mean dose of meperidine (mg) D 89.7±28.1 vs P 100.7±30.8 ($p=0.003$) D 3.46±1.15 vs P 4.01±1.27 ($p<0.001$) Duration of CT No significant difference between group D and P Recovery time(min) D 48.6±16.8 vs P 48.9±16.9 ($p=0.06$) Discharge time(min) D 90.1±26 vs P 89.1±21 ($p=0.76$) Interruption for patient discomfort D 0.108±0.31 *vs* P 0.086±0.28 ($p<0.5561$) 2 patients (1 from group D and 1 from group P) had incomplete colonoscopy because multiple interruptions Complications No significant different between the group D and P Group D: Hypoxia for 1 patient; bradycardia and hypotension for 1 patient Group P: Hypotension for 5 patient; hypoxia for 6 patient	**II** The addition of diphenhydramine to routine sedation significantly improved the overall sedation scores as assessed by the endoscopists and the nurses. Similarly, patient assessments of the overall sedation also favored the diphenhydramine group. Other measures, including recollection of the procedure and pain scores as reported by the patient, were significantly better in the diphenhydramine group. Our data strongly suggest that diphenhydramine can be used effectively as an adjunct, providing overall superior sedation when compared with the use of traditional sedatives alone.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: yes; blindness of clinical staff: yes; blindness of outcome assessor: yes; lost at follow up: 1 from group D and 1 from group P due to incomplete colonoscopy.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Arici G, 2003	The aim of this study was to compare the effectiveness of remifentanil/ midazolam, and tramadol/ midazolam for iv sedation and analgesia during colonoscopy. Randomised controlled trial Turkey	36 patients (age range 18-65 years) undergoing colonoscopy were randomised to receive midazolam plus remifentalin (group R=18) or midazolam plus tramadol (group T=18)	Colonoscopy with sedation using midazolam 1 mg intravenous followed by: R: midazolam plus remifentalin (remifentanil bolus (10 microg) and infusion 0.03 microg kg(-1) min(-1) were administered until adequate sedation level) (n=18) or T: midazolam plus tramadol (50 mg) (n=18)	Haemodynamic variables, respiratory depression, level of sedation, postoperative recovery, patient and gastroenterologist satisfaction	Colonoscopy was carried out successfully in all patients. There were no episodes of desaturation or airway compromise. Haemodynamic parameters No significant difference for in both groups. Sistolic arterial and diastolic arterial pressures were increased at 10 and 15 minutes in all patients ($p<0.05$). No significant changes in heart rate in both groups. The level of sedation in group R was higher than group T during colonoscopy. The patients in group T had higher pain scores (10-point numerical rating scale). Gastroenterologist satisfaction and patient satisfaction were similar in both groups.	II Our results suggests that, sedoanalgesia with midazolam/remi fentanil may be an alternative to sedoanalgesia with midazolam/tra madol for colonoscopy..

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Zakko S.F, 1999	The goals were (1) to determine clinically equivalent doses for midazolam and diazepam in human subjects; (2) to determine the effect of age and gender on the sedative dose of these medications; and (3) to determine the effect of these clinically equivalent doses of midazolam and diazepam on resting ventilation and oxygenation. Randomised controlled trial (double blind). Farmington, Connecticut	100 patients (aged 22-83; 2 eliminated for equipment malfunction) undergoing colonoscopy were randomised to receive meperidine followed by midazolam (group M: 23 men and 26 women; mean age 59 ± 2) or diazepam (group D: 27 men and 22 women; mean age 58 ± 2). No difference among the group for age, gender, number of patients who had taken a benzodiazepine within the previous month.	Colonoscopy with sedation using meperidine (25 to 50 mg) followed by M: incremental doses of either midazolam (n=49) D: diazepam to an identical end point of slurred speech and/or ptosis (n=49).	Level of sedation (OAAS scale), end-tidal pressure of carbon dioxide ($PetCO_2$), oxygen saturation (by $SpO2$), duration of CT and recovery.	Mean duration of colonoscopy (min) M 43±3 *vs* D 42±3 *(p ns)* Duration of recovery (min) M 22±2 *vs* D 22±2 *(p ns)* Mean sedation score M 3.6±0.1 vs D 3.6±0.1 Dose (mg/kg) No difference between group for the dose of meperidine. Midazolam 0.031 ± 0.002 vs Diazepam 0.106 ± 0.009 (Midazolam was 3.4 times more potent than diazepam) Significant negative correlation between age and diazepam dose (regression coefficient = $-1.34 \cdot \cdot 10^{-3}$ mg $\cdot \cdot kg^{-1} \cdot \cdot y^{-1}$, $p < 0.05$). No significant correlation between age and midazolam dose. No significant correlation between gender and diazepam dose. Midazolam dose women 0.038 ± 0.02 vs men 0.023 ± 0.01 *(p<0.05)* $PetCO_2$ Values significantly higher in group M than group D (p<0.05) in the first 45 minutes after injection. Sp O_2 <90% M 10.2±1.9 min vs D 11.5±2 min (*p* ns) Sp O_2 values significantly lower than baseline for 80 minutes after each agent (p<0.05)	**II** Midazolam was 3.4 times more potent than diazepam. The duration of oxygen desaturation emphasizes the importance of monitoring SpO2 until ventilation and oxygenation have recovered. Although the degree of hypoxemia was comparable, midazolam led to higher end-tidal carbon dioxide tensions.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
					<u>Hypoxemia intervention</u> Intervention for 12 patients (M=4, D=8) before drug administration for Sp O_2<92% Intervention for 23 patients (M=12, D=11 p ns) after drug administration for SpO_2<85%	

Quality assessment: allocation concealment: adequate; blindness of patients: yes; blindness of clinical staff: yes; blindness of outcome assessor: yes; lost at follow up: 4 from group M and 8 from group D because Sp O_2<92% before drug administration.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Ginsberg G.G., 1992	To evaluate the efficacy of the currently recommended low doses of midazolam for conscious sedation compared with diazepam for colonoscopy. Prospective randomised, double-blind controlled trial Washington, USA	53 patients undergoing colonoscopy were randomised to receive diazepam plus meperidine (group A=24) or midazolam plus meperidine (group B=29)	Colonoscopy with sedation using : A: diazepam plus meperidine (n=24) or B: midazolam plus meperidine (n=29) Each agent was administered in a fixed ratio dose in combination with meperidine, and titrated incrementally to allow for adequate sedation prior to initiating and during the procedure.	Level of sedation, amnesia score, recovery time, procedure pain.	Level of sedation The currently recommended starting dose of midazolam (0.03 mg/kg) proved to be very appropriate for pre-medication. In contrast, the currently recommended starting dose of diazepam (0.10 mg/kg) proved excessive in 21% of patients (especially in those aged >65). The low initial and incremental doses of midazolam compared favorably with diazepam in all efficacy parameters studied and exceeded diazepam in post-procedure amnesia scores (p = 0.01). The sedative effects of midazolam at these lower doses were not lost despite long duration procedures (>40 min). No significant difference for recovery time and procedure time between the group A and B	II We conclude that midazolam, given in small incremental doses, in combination with meperidine, produces effective conscious sedation for colonoscopy and exceeds diazepam in its amnestic effect.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
DiPalma J.A., 1995	To determine whether the narcotic alfentanil, a relatively new fentanyl derivative with rapid onset of action and offset of activity, alone or in combination with midazolam has advantages over the traditional meperidine and midazolam regimen for conscious sedation. Randomised controlled trial Alabama USA	35 patients undergoing colonoscopy were randomised to receive midazolam plus alfentanil (group A=11) or midazolam plus meperidine (group B=11) or placebo and alfentanil (group C=13)	Colonoscopy with sedation using : A: midazolam plus alfentanil (n=11) or B: midazolam plus meperidine (n=11) or C: placebo and alfentanil (n=13) The patients received an initial dose of narcotic and sedative with additional narcotics or sedatives administered as needed.	Recovery time, complications, desaturation, discomfort for patients, vital sign, oxygen saturations.	Subjects receiving no midazolam sedative (group C) had less <u>desaturation</u> and had the need for supplemental oxygen less often than those receiving alfentanil and midazolam (group A) or meperidine and midazolam (Group B). No differences as assessed by patient and colonoscopist for <u>tolerance and discomfort, procedure ease, recovery time, complications, electrocardiogram, and blood pressure</u>. Baseline evaluation did not predict the need for supplemental oxygen.	**II** We concluded that alfentanil, with or without a sedative, has no advantage over the commonly used meperidine and midazolam regimen.

5.8   Key performance indicators

5.8.1 Summary document

Silvia Minozzi, Clare Monk

CLINICAL QUESTION 13

What are the key performance indicators for a technically sound, high quality and safe procedure?

PICOS

P: General and screened populations undergoing colonoscopy or flexible sigmoidoscopy
I: Key performance indicators for colonoscopy or flexible sigmoidoscopy
C: Not applicable
O: Detection, description and evaluation, and decision-making and incomplete procedures
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

Searches were performed on MedLine and Embase, restricting the search to between 2000 and 2008. Pubmed
Free text search terms:
'colonoscopy AND performance indicators AND quality' identified 1 paper of interest.
'quality AND technical performance AND colonoscopy' identified 2 papers recommending quality indicators by Levin et al, 2005 and Rex et al, 2002.
Searches on Embase revealed the same papers that were found on pubmed.
We performed also a broader search on MedLine with the following strategy:
 (exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy)

RESULTS

Two guidelines on performance quality indicators (1,2), one retrospective (3) and one prospective study (4) have been retrieved.

One guideline on key performance indicators for colonoscopy was produced by the US Multi-Task Force on Colorectal Cancer endorsed by the American College of Gastroenterology, the American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. The ACP-ASIM representatives on the task force contributed to and approved the final document, but the ACP-ASIM did not review it at a society level (1).

The second was also produced by the US Multi-Task Force on Colorectal Cancer and endorsed by the American College of Gastroenterology, the American College of Physicians-American Society of Internal Medicine, the American Gastroenterological Association, and the American Society for

Gastrointestinal Endoscopy (ASGE). Investigators performing three large randomised clinical trials of FS provided additional expert opinion (prostate, lung, colorectal, and ovarian trial of the US National Cancer Institute (Robert E Schoen), the UK Flexible Sigmoidoscopy Trial (Wendy Atkin), and the Norwegian Colorectal Cancer Prevention trial (Geir Hoff). The focus of these recommendations was on the quality of FS in relation to screening and prevention of colorectal cancer and was published in 2005 (2).

The performance quality indicators for colonoscopy proposed are the following (1):

PRECAUTIONS
1. Identification of ASA class and appropriate action (goal: 100%).
2. Identification of anticoagulation and appropriate action (goal: 100%).
3. Appropriate action with regard to prophylactic antibiotics (goal: 100%).

INSERTION
1. Caecal intubation rates in all cases (90%) and in screening cases (95%).
2. Documentation in endoscopic reports of caecal intubation and visualized landmarks.

COLONOSCOPE WITHDRAWAL
1. Mean examination times (during duration of withdrawal phase). Goal: withdrawal times should average at least 6–10 min.
2. Adenoma prevalence rates detected during colonoscopy in persons undergoing first-time examinations. Goal: (25% in men older than 50 and 15% in women 50 or older.
3. Documentation of quality of bowel preparation. Goal: 100%.

BIOPSY AND POLYPECTOMY
1. Number and distribution of biopsy samples in ulcerative colitis and Crohn's colitis surveillance. Goal: four per 10-cm section of involved colon or approximately 30 biopsies in cases of panulcerative colitis.
2. Documentation of the size and shape distribution of benign polyps sent for surgical resection (as measured by the pathologist). Goal: mucosally based pedunculated polyps and sessile polyps of 2 cm in size should not be sent for surgical resection without an attempt at endoscopic resection or documentation of endoscopic inaccessibility.
3. Percentage of resected colon polyps recovered for pathological examination. Goal: _95%.

COMPLICATIONS
1. Percentage of cases with informed consent. Goal: 100%.
2. Percentage of cases with four principal adverse outcomes listed on the consent form or on an accompanying procedure or progress note. Goal: 100%.
3. Incidence of minor sedation reactions, such as unplanned reversal of sedation. Goal: <1 in 100.
4. Incidence of more serious adverse reactions, such as need for mask ventilation or endotracheal intubation. Goal: <1 in 300.
5. Incidence of perforation by type (mechanical, small polyp, large polyp). Goal:<1 per 1000; for screening exams, <1 per 2000.
6. Incidence of postpolypectomy bleeding (immediate and delayed) (goal, <1 per 100) cases involving polypectomy. The expected rate will vary, being higher in practices that remove large polyps and much lower in those practices that refer large polyps to others.

INTERACTING WITH PATHOLOGISTS
1. Percentage of adenomas with villous elements. Goal: <10%.
2. Reports using the terms carcinoma in situ or intramucosal adenocarcinoma. Goal: none.
3. Designation of the degree of dysplasia in adenomas as low grade or high grade. Goal: 100%.
4. Use of the terms mild, moderate, or severe to describe dysplasia and adenomas. Goal: none.
5. Adequate characterisation of malignant polyps (resection line "margin," degree of differentiation, presence or absence of vascular [or lymphatic] invasion). Goal: 100%.
The performance quality indicators for flexible sigmoidoscopy proposed are the following (25):
(1) Completion of adequate follow up colonoscopy on more than 90% of patients in whom it is indicated. (C: consensus based)
(2) Knowledge of recommended screening intervals and compliance with practice guidelines. (C)

(3) Adequate documentation of all lesions found on FS, allowing the colonoscopist to complete removal of unremoved lesions. (C)

(4) Annual performance reviews of clinicians performing FS, measuring complications, depth of insertion, and detection of polyps and cancer. (C)

(5) Identification and appropriate reaction with respect to anticoagulation and antibiotic prophylaxis. (E: evidence based)

(6) Average depth of sigmoidoscope insertion stating whether level reached is maximal insertion or after straightening the endoscope. (C)

(7) Documentation in endoscopic report of depth of insertion in cm (100%). (C)

(8) Patient satisfaction with the FS experience, including level of discomfort with the procedure (approximately 70% should be satisfied with the procedure). (E evidence based)

(9) Documentation of quality of bowel preparation. Goal = 100%. (E)

(10) Documentation of informed consent. Goal = 100%. (E)

(11) Complication rates following biopsy and polypectomy at FS. (E)

(12) Development and compliance with guidelines for the performance of FS by non-physicians, including training, supervision, and ongoing proctoring. (C)

(13) Knowledge of ASGE-SGNA guidelines on flexible endoscope reprocessing. (E)

(14) Compliance with policies for endoscope reprocessing. (E)

A retrospective study by Millan 2008 (3) has also been retrieved. It assessed the adenoma detection rate during colonoscopy and the factor associated with its variation among six staff endoscopists. Each endoscopist performed >250 examinations per year and had >1,000 total examinations. A wide variation in adenoma detection rates among experienced colonoscopists has been detected in the study. A clear correlation between the adenoma detection rate and withdrawal time of the procedure has also been found. The authors concluded that endoscopists should be aware of their adenoma detection rate, as a key for maintaining high-quality standards in colonoscopy.

One prospective study by Radaelli 2008 (4) assessed the factors linked to two key indicators of colonoscopy performance, i.e., caecal intubation and polyp diagnosis. By multivariate analysis the study found that the quality of bowel preparation and the routine use of sedation/analgesia are the strongest predictors of both caecal intubation and polyp detection. The endoscopist experience and the colonoscopy volume of centers are other factors that decisively influence the quality of colonoscopy. Authors concluded that adopting strategies to implement the routine use of sedation and improve intestinal preparation, and increasing focus on endoscopist training should represent the targets of quality improvement programs.

CONCLUSIONS

The key performance indicators outlined in the guidelines are reported in the results section. No level of evidence supporting the quality performance indicators proposed by the guidelines can be stated because no clear description of the method used to retrieve, include/exclude, assess the methodological quality of included studies are reported in the guidelines. The methods used to analyse and synthesise the chosen studies are not discussed. No grading levels of evidence were provided.

The quality of bowel preparation, the use of sedation /analgesia, the endoscopist experience and the colonoscopy volume centres are factors strongly predicting of both caecal intubation rate and polyp detection rate (LEVEL OF EVIDENCE III)

REFERENCES

1. Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, Kirk LM, Litlin S, Lieberman DA, Waye JD, Church J, Marshall JB & Riddell RH (2002), Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer, *Am.J.Gastroenterol.*, vol. 97, no. 6, pp. 1296-1308.

2. Levin TR, Farraye FA, Schoen RE, Hoff G, Atkin W, Bond JH, Winawer S, Burt RW, Johnson DA, Kirk LM, Litin SC & Rex DK (2005), Quality in the technical performance of screening flexible sigmoidoscopy: recommendations of an international multi-society task group, *Gut*, vol. 54, no. 6, pp. 807-813.

3. Millan MS, Gross P, Manilich E & Church JM (2008), Adenoma detection rate: the real indicator of quality in colonoscopy, *Dis Colon Rectum*, vol. 51, no. 8, pp. 1217-1220.

4. Radaelli F, Meucci G, Sgroi G & Minoli G (2008), Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators, *Am J Gastroenterol.*, vol. 103, no. 5, pp. 1122-1130.

5.8.2   Evidence tables (see 5.10.2)

5.9   Completeness of colonoscopy

5.9.1   Summary document

Silvia Minozzi, Clare Monk

CLINICAL QUESTION 14

What is the most reliable method used to identify completeness of colonoscopy?

PICOS

P: General and screened populations undergoing colonoscopy
I: Methods used to identify completeness of colonoscopy
C: Not applicable
O: Completeness
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

Searches were performed on MedLine and Embase, restricting the search to between 2000 and 2008.
Pubmed
Free text search terms:
'determining completion of colonoscopy' identified one relevant paper.
'method AND determination of complete colonoscopy' returned no relevant papers.
'cecum AND determination of complete colonoscopy' returned no relevant papers.
'complete caecal intubation AND determination of complete colonoscopy' returned no relevant papers.
No further papers were identified on Embase using identical search terms

RESULTS

Only one study was retrieved. Thuraisingam 2008 assessed the sensitivity and specificity of two endoscopic photographs. The second photograph could be of any another caecal landmark, the terminal ileum or a different view of the valve. As Reference standard a brief video clip of the completed colonoscopy (approximately 30 s to 2 min duration) that could demonstrate ileal intubation or the caecal landmarks to another endoscopist later reviewed by a second study endoscopist to confirm that complete colonoscopy had been carried out was used. The study was performed on 80 colonoscopies. 20 pairs of photographs were also taken from another colonic site that could potentially be misinterpreted as the caecum, for example, hepatic flexure 32 reviewers assessed the 100 photographic pairs, blinded to their origin. The study found a sensitivity of 51.4% and a specificity of 89.2% which were considered too low to be used for reliably documenting colonoscopy completion

CONCLUSIONS

Only one study was retrieved assessing specificity and sensitivity of a pair of photograph to assess the completeness of colonoscopy. This method seems to have too low accuracy to be used in clinical practice. (LEVEL OF EVIDENCE III)

REFERENCE

1. Thuraisingam AI, Brown JB and Anderson JT. What are the sensitivity and specificity of endoscopic photographs in determining completion of colonoscopy? Results from an online questionnaire. European Journal of Gastroenterology & Hepatology 2008, 20:567–57

5.9.2 Evidence tables (see 5.10.2)

5.10 Completeness of flexible sigmoidoscopy

5.10.1 Summary document

Silvia Minozzi, Clare Monk,

CLINICAL QUESTION 15

What defines a complete examination of FS (up to splenic flexure)? Does the imager improve the determination of completeness?

PICOS

P: General and screened populations undergoing flexible sigmoidoscopy
I: Methods and criteria for defining completeness of flexible sigmoidoscopy
C: Not applicable
O: Completeness
S: RCTs, systematic and narrative reviews, cohort and case control studies

SEARCH METHOD

Pubmed
Free text search terms: 'complete examination AND flexible sigmoidoscopy'
This search identified no relevant papers. The search was also checked by an expert in the field and none were deemed relevant.
Free text search: 'complete examination AND splenic flexure AND flexible sigmoidoscopy' returned no relevant search results.
The paper by Painter et al, 1999 was recommended by an expert in the field.
Searches on Embase returned no relevant search results

RESULTS

Only one study was retrieved in which Painter 1999 assessed the depth of insertion at flexible sigmoidoscopy by magnetic resonance imaging Two studies were performed. In the first (study 1), magnetic endoscopic imaging was used to determine the final depth of insertion at non-sedated, screening flexible sigmoidoscopy. In the second (study 2), "real-time" imaging was utilised to determine sigmoid looping and the anatomical location of the endoscope tip after 60cm of instrument had been inserted. In study 1 in 61% of patients the imaging system showed that the descending colon had not been visualised by the end of the procedure. In study 2 after 60cm of instrument had been inserted, the splenic flexure or beyond was reached in 29% and the descending colon in 9%, whilst in 62% the endoscope tip had not passed beyond the sigmoid/descending colon junction.

CONCLUSIONS

Magnetic resonance imaging showed that in more than one half of patients the descending colon had not been visualized. Also after 60 cm of insertion the splenic flexure was reached only in 29% of the patients (LEVEL OF EVIDENCE V).

REFERENCE

1. Painter J, Saunders DB, Bell GD et al. Depth of insertion at flexible sigmoidoscopy: implication for colorectal cancer screening and instrument design. Endoscopy 1999;31:227-231

5.10.2 Evidence tables

Author, publication year	Objective Study design	Methods	Quality improvement targets	Conclusions and final recommendations
Rex et al. 2002 US Multi-Society Task Force on Colorectal Cancer	To provide evidence- and consensus-based standards for the performance of high quality colonoscopy. These recommendations address the appropriate indications and intervals for colonoscopy and polypectomy, the technical performance of colonoscopy, biopsy and polypectomy, complications of colonoscopy, and the interaction of colonoscopists with pathologists. Clinical guideline USA Recommendations reviewed and endorsed by the American College of Gastroenterology, The American Gastroenterological Association, and The American Society for Gastrointestinal Endoscopy. the ACP-ASIM representatives to the task force contributed to and approved the final document, the ACP-ASIM did not review it at a society level	Methodology for the bibliograpchic search and production of the recommendation not reported. Only stated that it was a consensus and evidence based guideline	PRECAUTIONS 1. Identification of ASA class and appropriate action (goal: 100%). 2. Identification of anticoagulation and appropriate action (goal: 100%). 3. Appropriate action with regard to prophylactic antibiotics (goal: 100%). INSERTION 1. Caecal intubation rates in all cases (90%) and in screening cases (95%). 2. Documentation in endoscopic reports of caecal intubation and visualized landmarks. COLONOSCOPE WITHDRAWAL 1. Mean examination times (during duration of withdrawal phase). Goal: withdrawal times should average *at least* 6–10 min. 2. Adenoma prevalence rates detected during colonoscopy in persons undergoing first-time examinations. Goal: (25% in men older than 50 and 15% in women 50 or older. 3. Documentation of quality of bowel preparation. Goal: 100%. BIOPSY AND POLYPECTOMY 1. Number and distribution of biopsy samples in ulcerative colitis and Crohn's colitis surveillance. Goal: four per 10-cm section of involved colon or approximately 30 biopsies in cases of panulcerative colitis. 2. Documentation of the size and shape distribution of benign polyps sent for surgical resection (as measured by the pathologist). Goal: mucosally based pedunculated polyps and sessile polyps of 2 cm in size should not be sent for surgical resection without an attempt at endoscopic resection or documentation of endoscopic inaccessibility. 3. Percentage of resected colon polyps recovered for pathological examination. Goal: 95%.	Appropriate use of colonoscopy can reduce colorectal cancer mortality and prevent colorectal cancers. The effectiveness of colonoscopy depends on the quality of examination. Evidence for variable performance of colonoscopy indicates that patient outcomes could be improved by a constructive process of continuous quality improvement that educates endoscopists in optimal colonoscopic techniques, procedure documentation, interpretation of pathological findings, and scheduling of appropriate follow-up examinations, and pathologists in the appropriate reporting of pathological findings. Continuous quality improvement is an integral part of a colonoscopy program. The task force recommends that these targets be periodically reviewed in continuous quality improvement programs. Findings of deficient performance can be used to educate colonoscopists and pathologists, and additional monitoring can be undertaken to document improvement in performance.

Author, publication year	Objective Study design	Methods	Quality improvement targets	Conclusions and final recommendations
			COMPLICATIONS 1. Percentage of cases with informed consent. Goal: 100%. 2. Percentage of cases with four principal adverse outcomes listed on the consent form or on an accompanying procedure or progress note. Goal: 100%. 3. Incidence of minor sedation reactions, such as unplanned reversal of sedation. Goal: <1 in 100. 4. Incidence of more serious adverse reactions, such as need for mask ventilation or endotracheal intubation. Goal:<_1 in 300. 5. Incidence of perforation by type (mechanical, small polyp, large polyp). Goal: <1 per 1000; for screening exams,<1 per 2000. 6. Incidence of postpolypectomy bleeding (immediate and delayed) (goal, <1 per 100) cases involving polypectomy. The expected rate will vary, being higher in practices that remove large polyps and much lower in those practices that refer large polyps to others. INTERACTING WITH PATHOLOGISTS 1. Percentage of adenomas with villous elements. Goal: <10%. 2. Reports using the terms *carcinoma in situ* or *intramucosal adenocarcinoma.* Goal: none. 3. Designation of the degree of dysplasia in adenomas as *low grade* or *high grade.* Goal: 100%. 4. Use of the terms *mild, moderate,* or *severe* to describe dysplasia and adenomas. Goal: none. 5. Adequate characterisation of malignant polyps (resection line "margin," degree of differentiation, presence or absence of vascular [or lymphatic] invasion). Goal: 100%.	

Quality assessment: Quality recommendations presented narratively based on literature review. Description of the clinical specialisation of the members of the panel author of the guideline provided Search strategy not described. Inclusion criteria of primary studies not provided. The method used to analyse and synthesise the evidence to reach a consensus is not stated. Recommendations are provided as continuous quality improvement targets and are not graded according to the level of evidence. A complete reference list is provided.

Author, publication year	Study objective Study design	Methods	Quality Improvement Targets	Conclusions
Levin et al. Gut 2005 US Multi-Society Task Force on Colorectal Cancer	We propose a set of consensus and evidence based recommendations to assist the development of continuous quality improvement programmes around the delivery of FS for colorectal cancer screening. Clinical guideline USA endorsed by the American College of Gastroenterology, the American College of Physicians-American Society of Internal Medicine, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy (ASGE). Investigators performing three large randomised clinical trials of FS provided additional expert opinion (prostate, lung, colorectal, and ovarian trial of the US National Cancer Institute (Robert E Schoen), the UK Flexible Sigmoidoscopy Trial (Wendy Atkin), and the Norwegian Colorectal Cancer Prevention trial (Geir Hoff).	Task Force members developed a list of major categories to be included. Medline search 1980-july 2004. Reference lists of identified articles were scanned for other articles of interest. Each author had an opportunity to review drafts of this position paper and had an opportunity to make meaningful revisions in the content. Grading of the recommendation: C: consensus based E: evidence based	(1) Completion of adequate follow up colonoscopy on more than 90% of patients in whom it is indicated. (C) (2) Knowledge of recommended screening intervals and compliance with practice guidelines. (C) (3) Adequate documentation of all lesions found on FS, allowing the colonoscopist to complete removal of unremoved lesions. (C) (4) Annual performance reviews of clinicians performing FS, measuring complications, depth of insertion, and detection of polyps and cancer. (C) (5) Identification and appropriate reaction with respect to anticoagulation and antibiotic prophylaxis. (E) (6) Average depth of sigmoidoscope insertion stating whether level reached is maximal insertion or after straightening the endoscope. (C) (7) Documentation in endoscopic report of depth of insertion in cm (100%). (C) (8) Patient satisfaction with the FS experience, including level of discomfort with the procedure (approximately 70% should be satisfied with the procedure). (E) (9) Documentation of quality of bowel preparation. Goal = 100%. (E) (10) Documentation of informed consent. Goal = 100%. (E) (11) Complication rates following biopsy and polypectomy at FS. (E) (12) Development and compliance with guidelines for the performance of FS by non-physicians, including training, supervision, and ongoing proctoring. (C) (13) Knowledge of ASGE-SGNA guidelines on flexible endoscope reprocessing. (E) (14) Compliance with policies for endoscope reprocessing. (E)	FS can be delivered in high volume, by a variety of examiners, safely, and with high patient satisfaction. The effectiveness of FS depends on the quality of examination. A constructive process of continuous quality improvement that educates endoscopists in optimal technique, procedure documentation, specimen acquisition, and endoscope reprocessing could improve patient outcomes. The Task Force recommends that all of the targets recommended be periodically reviewed in continuous quality improvement programmes. Findings of deficient performance can be used to educate endoscopists, and additional monitoring can be undertaken to document improvement in performance..

Quality assessment: Description of the clinical specialisation of the members of the panel author of the guideline provided. Search strategy described (database, years and language restriction). Language restriction: only English language articles included. Inclusion and exclusion criteria not defined. Method used to analyse and synthesise the evidence and to reach the consensus among the panellist to elaborate the recommendation described. Quality improvement targets graded as consensus (C) or evidence (E) based recommendations. A complete reference list is provided.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Millan 2008	To detect the adenoma detection rates of six colorectal surgeons to provide insight into the range of adenoma detection rates and the factors that influence them. Retrospective survey	A review of colonoscopies from January 1998 to December 2004 using the prospective colonoscopy database of the Cleveland Clinic Department of Colorectal Surgery was performed. All staff colorectal surgeons with >1 000 exams performed during this period were included USA	Colonosocpy	Completion rate adenoma detection rate (ADR) times of insertion and withdrawal	Six staff endoscopists were included in this study. Each endoscopist performed >250 examinations per year and had >1,000 total examinations. The total number of colonoscopies performed during this period was 16,335. Completion rate: 96.5% (range, 94.8–97.9) Adenoma detection rate: 21% (range, 14.2–27.4) withdrawal time: range:5.5 - 14.1 minutes regression of withdrawal time against adenoma detection rate produced an r2 of 0.975 (P <0.0016)	**V** A wide variation in adenoma detection rates among experienced colonoscopists has been detected. A clear correlation between the adenoma detection rate and withdrawal time of the procedure has also been found.. The study is limited by the relatively low number of endoscopists; however, has been shown that withdrawal times and adenoma detection rates can vary widely Adenoma detection rate is an important colonoscopy quality indicator, and there are wide variations in detection between colonoscopists Endoscopists should be aware of their adenoma detection rate, as a key for maintaining high-quality standards in colonoscopy.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Radaelli 2008	To assess the factors linked to two key indicators of colonoscopy performance, *i.e.*, caecal intubation and polyp diagnosis Prospective cohort study	Consecutives colonoscopies performed over a 2-wk period in 278 unselected practice sites were prospectively evaluated. A multivariate model was developed to identify Determinants of the performance indicators of colonoscopy. Italy	Colonoscopies	(a) caecal intubation rate (b) polyp detection rate By considering caecal intubation and detection of at least one polyp as the variables to assess the technical performance of the examination, we calculated the proportion of colonoscopies in which the cecum was reached, and for which one polyp was diagnosed in relation to the number of examinations done for the other variables: colonoscopy setting (type of center: complex operative unit, simple operative unit, or outpatient unit; annual workload of colonoscopies: ≤1,000 or >1,000), patient characteristics (sex and age ≤35, 36–64, 65–75, or >75), endoscopist colonoscopy volume (<300, 300–500, or >500), indication for the examination (abdominal pain, rectal bleeding, bloody diarrhea, chronic diarrhea, constipation, screening, or follow-up), sedation (none, benzodiazepine IV, benzodiazepine + narcotics IV, propofol, or other sedation regimens), and quality of bowel cleansing (excellent, good, poor, or inadequate). Logistic regression analysis was then done to establish which of the above variables was significant for caecal intubation and detection of at least one polyp. The final models included only the significant ones	Caecal intubation rate: 80.7% polyp detection rate 27.3%. Multivariate analysis showed that the strongest predictors of caecal intubation were the quality of bowel preparation (inadequate *vs* excellent: odds ratio [OR] 0.013, 95% confidence interval [CI] 0.009–0.018; fair *vs* excellent: OR 0.246, 95% CI 0.209–0.290; and good *vs* excellent: OR 0.586, 95% CI 0.514–0.667) and the use of sedation (IV benzodiazepines *vs* no sedation: OR 1.460, 95% CI 1.282–1.663; IV benzodiazepines and narcotics *vs* no sedation: OR 2.128, 95% CI 1.776–2.565; and propofol *vs* no sedation: OR 2.355, 95% CI 1.590–3.488). The colonoscopy setting (workload and organisational complexity of the center) and the endoscopist colonoscopy volume were other factors independently correlated with completion of the procedure. Detection of polyps partially depended on the quality of bowel cleansing (inadequate *vs* excellent: OR 0.511, 95% CI 0.404–0.647) and use of sedation (OR 1.172, 95% CI 1.074–1.286).	III The quality of bowel preparation and the routine use of sedation/analgesia are the strongest predictors of both caecal intubation and polyp detection. The endoscopist experience and the colonoscopy volume of centers are other factors that decisively influence the quality of colonoscopy. Adopting strategies to implement the routine use of sedation and improve intestinal preparation, and increasing focus on endoscopist training should represent the targets of quality improvement programs.

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Thuraisingham 2008	The primary aim of this study was to calculate the diagnostic specificity and sensitivity of a pair of photographs in confirming complete colonoscopy. Diagnostic accuracy study UK	80 pairs of photographs were taken from completed colonoscopies, 20 pairs of photographs were also taken from another colonic site that could potentially be misinterpreted as the caecum, for example, hepatic flexure. 32 reviewers assessed the 100 photographic pairs, blinded to their origin, and were asked 'Taking both photographs into account, are you convinced that complete colonoscopy has been performed?'	Index test: two endoscopic photographs. The second photograph could be of any other caecal landmark, the terminal ileum or a different view of the valve. Reference standard: a brief video clip of the completed colonoscopy (approximately 30 s to 2 min duration) that could demonstrate ileal intubation or the caecal landmarks to another endoscopist later reviewed by a second study endoscopist to confirm that complete colonoscopy had been carried out	Sensitivity specificity	Sensitivity: 51.4% (95%CI: 49.5–53.3%) specificity: 89.2% (95%CI: 86.8–91.6%).	III Both the sensitivity and the specificity of a pair of endoscopic photographs are too low to be used for reliably documenting colonoscopy completion

Quality assessment: no description if the spectrum of patients were representatives of the patients who will receive the test in practice. Patients selection criteria not described. All the samples received the reference standard (avoidance of verification bias). Index test and reference standard described.

Author, publication year	Study objective Study design	Study Participants	Outcomes	Results	Conclusion Level of evidence
Painter et al. 1999	The aim of this study was to assess the depth of insertion at flexible sigmoidoscopy by magnetic resonance imaging Cross-sectional study Two separate studies were done. In the first (study 1), magnetic endoscopic imaging was used to determine the final depth of insertion at non-sedated, screening flexible sigmoidoscopy. In the second (study 2), "real-time" imaging was utilised to determine sigmoid looping and the anatomical location of the endoscope tip after 60cm of instrument had been inserted during total or limited colonoscopy	117 consecutive average risk patients, aged 55-65 years participated in study 1, and 136 patients underwent either limited, (33) or attempted total colonoscopy (103) in study 2.	Final depth of insertion visualized by magnetic resonance imaging in study 1 Percent of examination reaching the splenic flexure after 60 cm of insertion in study 2	In study 1 the median insertion distance was 52cm range 20-58. In 61% of patients the imaging system showed that the descending colon had not been visualised by the end of the procedure. Failure to reach the sigmoid/descending junction occurred in 29 (24%) patients. Reasons for failure included: • poor tolerance of the procedure due to pain (23 patients) • inadequate preparation (3 patients) • excessive looping (3 patients). In study 2, after 60cm of instrument had been inserted, the splenic flexure or beyond was reached in 29% and the descending colon in 9%, whilst in 62% the endoscope tip had not passed beyond the sigmoid/descending colon junction	**V** Examination of the entire sigmoid was not achieved in approximately one quarter of patients undergoing screening flexible sigmoidoscopy, mainly because of discomfort. The descending colon is intubated in a minority of cases (using standard instruments), even after 60cm has been inserted. Alternative instruments with different shaft characteristics (floppy, narrow calibre, 80-100cm in length) may be necessary to ensure deeper routine intubation in nonsedated patients.

5.11 Criteria for postponing polypectomy in patients taking anticoagulants/ antiaggregants

Please see chapter 8 for this document and the corresponding evidence tables.

5.12 Additional evidence tables prepared after December 2009

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Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Adler A., 2009	To compare the NBI with white light colonoscopy in adenoma detection rates. Multicenter randomised controlled trial Germany	1,256 outpatients undergoing screening colonoscopy (men:women, 47%:53%; mean age, 64.4 y) were randomised to HDTV screening colonoscopy with either NBI (NBI group: 47% male; mean age 64.8± 6.5) or white-light imaging on instrument withdrawal exclusively (control group: 47,9% male; mean age 64.3± 7.1) Colonoscopies were performed in 5 private gastroenterology practices and included 6 experienced examiners (>10,000 colonoscopies). No significant difference between groups with regard to gender and age.	Screening colonoscopy with wide-angle colonoscopes with high definition television (HDTV) imaging with either using: NBI group: the NBI mode (n=625) or Control group: white-light imaging (n=631).	ADR (number of adenomas/number of patients examined) in the 2 groups; total number of all polyps (adenomas/hyperplastic polyps), hyperplastic polyps.	**All polyps** N NBI group= 346 Control group =332 *p=ns* Patients with adenomas NBI group= 33.4% Control group =36.9% *p=ns* **Adenomas** N NBI group= 200 Control group =216 *p=ns* Patients with adenomas NBI group= 22.4% Control group =21.7% *p=ns* ADR NBI group= 0.32 Control group =0.346 *p=ns* No differences between the 2 groups in the ADR, when analysed for subgroups in relation to size, form, and location . and age and sex, too. Adenomas <10 mm NBI group= 178 Control group =187 *p=ns* **Hyperplastic polyps** N NBI group= 146 Control group =116 *p=0.03* Hyperplastic polyps <10 mm NBI group= 139 Control group =113 *p=0.05*	**II** This large randomised trial in a homogeneous private practice screening setting could not show any objective advantage of the NBI technique over white-light high definition television imaging in terms of improved adenoma detection rate, either overall or in subgroups.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: no; 38 patients excluded from the analysis (including 9 carcinomas).

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Aoun 2008	To compare the efficacy of two regimens of bowel preparation before colonoscopy: a whole dose of polyethylene glycol electrolyte solution (PEG-E), with diet restriction vs. a split dose with no diet restriction. **RCT**	141 patients (ages 20-84 years, 81 men) seen in the ambulatory outpatient clinic of the American University of Beirut Medical Center who required elective colonoscopies	(Group A) (N: 73) : 4 L PEG-E, along with a liquid diet the day before colonoscopy Group B (n:68) 2 L PEG-E with a regular diet the day before colonoscopy followed by another 2 L PEG-E on the day of the procedure	**Acceptability by patients** (willingness to take the same regimen again if needed) **Adherence to regimen** **Bowel cleansing**	**Acceptability by patients** (willingness to take the same regimen again if needed) Group A: 75% Group B: 84% **Adherence to regimen** Group A: 78% Group B: 90% **Bowel cleansing** Satisfactory Group A: 56.2% Group B: 76.5% P: 0.011	**II** the split-dose regimen with no dietary restrictions offers major benefits in clinical practice. These include a significantly greater quality of colon cleansing, with no additional adverse effects or discomfort to the patient. With the current design of this study, we cannot determine whether the improved results in the split-dose arm were because of splitting the dose of PEG-E or the lack of dietary restriction, although, intuitively, the latter is more likely to have a negative instead of a positive influence on the colonoscopy preparation

Quality assessment: adequate sequence generation: yes; adequate allocation concealment: yes; blinding of participants and providers: not possible; blinding of outcome assessor: yes; intention to treat analysis or few and balanced lost at follow up: no drop out from the study.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Barclay R.L., 2006	To assess the performance of screening colonoscopy in everyday practice, we conducted a study of the rates of detection of adenomas and the amount of time taken to withdraw the colonoscope among endoscopists in a large community-based practice. Retrospective cohort study Illinois	2,053 consecutive patients who underwent screening colonoscopy and who had not previously undergone colonoscopy in a large community-based gastroenterology practice during a 15-month period. The 12 endoscopists who performed colonoscopies, had performed a minimum of 3000 colonoscopies before this study began.	Screening colonoscopy	rate of adenoma detection and rates of detection of advanced lesions by colonoscopic withdrawal times	**Mean colonoscopic insertion time** = 7.2±4.4 minutes **Withdrawal Time for procedures in which polyps were Removed=** 10.6±5.8 minutes **Withdrawal Time for procedures with no polyps removed=** 6.3±3.9 minutes (range 3.1-16.8) Procedures in which no polyps were removed: **% subjects with adenomas** All physicians= 24.2± 8.3 Less than 6 minutes= 11.8± 2.2 6 minutes or longer= 28.3± 4.0 *p<0.001* **N adenomas per subject screened** All physicians= 0.50± 0.26 Less than 6 minutes= 0.17± 0.07 6 minutes or longer= 0.61±0.20 *p=0.006* **% subjects with advanced neoplasia** All physicians= 5.5±2.3 Less than 6 minutes= 2.6±1.1 6 minutes or longer= 6.4±1.7 *p=0.005* **N advanced neoplastic lesion per subject screened** All physicians= 0.06±0.03 Less than 6 minutes= 0.03±0.01 6 minutes or longer=0.07±0.02 p=0.005 **% subjects with hyperplasia** All physicians= 22.6±12.1 Less than 6 minutes= 10.2±4.2 6 minutes or longer= 26.8±10.9 *p=0.03* Strong and significant correlation between rates of detection of adenomas and withdrawal times.	**III** Greater rates of detection of adenomas among endoscopists who had longer mean times for withdrawal of the colonoscope.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record; adjustment for multiple prognostic factor.

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Bretthauer 2005	to investigate the risk of CO2 retention when using CO2 insufflation during colonoscopy in sedated patients, in comparison with unsedated patients. In addition, the amount of pain experienced due to colonoscopy was assessed in relation to the type of insufflation gas used **RCT**	103 consecutive patients un−dergoing colonoscopy. Patients under 15 years of age and those unable to understand information about the purpose of the study were excluded from participation. Patients with severe chronic obstructive pulmonary disease (COPD) and known CO2 retention were also excluded.	**Group1**: air insufflatoin (n: 51) **Group 2**: CO2 insufflation (n.: 52)	**ET CO2** ETCO2 has been shown to provide adequate approximations for arterial Pco2 in spontaneously breathing adults and is therefore a good noninvasive method of measuring arterial Pco2 **pain** questionnaire given to the participants immediately after the examination, to be filled in at home the day after the examination. A 100−mm visual analogue scale (VAS) was used, ranging from "no pain" on the left end to "pain as bad as it could be" at the right	**ET CO2** There were no statistically significant differences between the two groups at any of the measurement points Pain mean amount of pain 1 h after colonoscopy Air group: 23 mm Co2 group : 4 mm P: 0.001	**II** CO2 insufflation during colonoscopy is superior to air insufflation in relation to the pain experienced after the procedure. CO2 insufflation does not lead to a clinically significant rise in ETCO2 levels, even in patients receiving sedation during the procedure.

Quality assessment: adequate sequence generation: not reported; adequate allocation concealment: yes; whole day colonoscopy sessions rather than individual patient swere randomly assigned for CO2 or air insufflation, in order to avoid unblinding due to changes in the gas setup between patients. blinding of participants and providers: yes; blinding of outcome assessor: yes; intention to treat analysis or few and balanced lost at follow up: no drop out from the study

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Burke C.A., 2010	To compare the difference in the detection of individuals with polyps, adenomas, or high-risk adenoma features between high resolution, high-definition colonoscopes (HD) and conventional colonoscopes (CC); and also compared the difference in detection of individuals with clinically insignificant colonic lesions, ≥2, <6-mm hyperplastic polyps between HD and CC. Prospective cohort study USA	852 patients (59.7±12.3 years and 61.5% males) undergoing colonoscopy at clevelan Clinic from 2007 to 2008.	HD colonoscopy vs CC colonoscopy: 426 patients who underwent HD were compared to a cohort of 426 individuals who underwent CC after matching by gender, age (±5 years).	Polyps detection rate and risk classification between groups	**Subjects with polyps, n(%)** <u>HD:</u> 170 (39.9) <u>CC:</u> 157 (36.9) p=0.34 **Subjects with adenomas, n(%)** <u>HD:</u> 105 (24.7) <u>CC:</u> 93 (21.9) p=0.36 **Subjects classified as high risk, n(%)** <u>HD:</u> 24 (5.7) <u>CC:</u> 19(4.5) p=0.43 **Subjects with ≥ 3 polyps, n(%)** <u>HD:</u> 52 (12.2) <u>CC:</u> 40(9.4) p=0.16 **Subjects with ≥ 3, <6-mm adenomas, n(%)** <u>HD:</u> 10(2.4) <u>CC:</u> 3(0.70) p=0.050 **Subjects with ≥ 2, <6-mm hyperplastic polyps, n(%)** <u>HD:</u> 24(5.6) <u>CC:</u> 24(5.6) p=0.99 **Number of polyps per patient, mean±sd** <u>HD:</u> 0.9 ± (1.4) <u>CC:</u>0.8±(1.5)p=0.36 **Number of adenomasper patient, mean±sd** <u>HD:</u> 0.4± (0.8) <u>CC:</u>0.3±(0.7)p=0.13 **Polyps detected, n** <u>HD:</u> 315 <u>CC:</u> 278	**III** HD colonoscopy does not increase the detection of individuals with polyps, adenomas, or highrisk adenoma features. HD does not increase the detection of individuals with clinically insignificant colonic lesions.

| | | | | | No difference in the overall distribution of the pathology (P = 0.85) or size (P = 0.37) of the lesions detected between groups.

Adematous, n (%)
HD *vs* CC: 167 (52) vs 134 (48)

Hyperplastic, n (%)
HD *vs* CC: 113 (36) vs 110 (40) | |

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non-exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding : but patients resulted well matched for most relevant prognostic factors with no significant differences between them. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
East 2008	To compare detection rates between high definition (HD) and standard definition (SD) colonoscopy. Prospective cohort study	130 Patients attending for routine colonoscopy aged 50–80 with intact colons, without known colitis, polyposis or major musculoskeletal problems	Group 1: HD colonoscopy (n.58) Group 2: SD colonoscopy (n:72) Patient allocation was dependant on colonoscope availability, not randomised. When both colonoscope types were available, HD scopes were chosen.	Proportion of patients with at least one adenoma. Numbers of adenomas, polyps and hyperplastic polyps detected Proportion of patients with at least one polyp or hyperplastic detected, Proportion of patients with at least three adenomas or polyps detected, Proportion and numbers of flat and∕ordiminutive adenomas (<6 mm) Numbers of proximal (caecum to the splenic flexure) and distal (splenic flexure to rectum) polyps and adenomas detected.	Proportion of patients with at least one adenoma **HD: 71% SD: 60% P: NS** Proportion of patients with at least three adenomas **HD: 29% SD: 18% P: NS** Numbers of adenomas **HD: 93 SD: 88 P: NS Number of polyps: HD: 145 SD: 155 P: NS** Proportion of patients with at least one polyps **HD: 81% SD: 798% P: NS** Proportion of patients with at least three polyps **HD: 48% SD: 33% P: NS**	**III** HD colonoscopy did not significantly increase adenoma or hyperplastic polyp detection compared to SD and a relatively modest effect size was excluded. High detection rates of adenomas and large proximal hyperplastic polyps appear possible with standard or HD colonoscopy with optimal operator technique. HD colonoscopy may have a role in cases where comprehensive detection of even diminutive lesions is paramount.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non-exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding : but patients resulted well matched for most relevant prognostic factors with no significant differences between them. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	Inclusion criteria	Intervention compared	Outcome	Results	Conclusion Level of evidence
Ladas 2007	To compare to discuss the indications and the types of bowel preparations for therapeutic colonoscopy, and to contribute recommendations for the adequate bowel preparation for colonoscopy with electrocautery. Only the data about the risk of colonic explosion were reported Systematic review	Studies published on colonic gas explosion. Without further specification	Colonoscopy or surgery	Type pf intervention associated with colonic explosion	**Cases identified: 20; 11 during surgery, 9 during colonoscopy** Argon plasma coagulation provided the initiating heat source in five of the nine colonoscopic cases, whereas the remaining four cases were associated with endoscopic polypectomy . 45% of gas explosion were complicated with colon perforation. Perforation was observed in all of the four polypectomy cases in two cases using argon plasma coagulation and in three cases during electrosurgery. One of the four perforations during polypectomy was fatal Bowel preparation by ingestion of a mannitol solution was used in 14 cases and of a cleansing solution containg sorbitol in one case. Preparation by enemas containg nofermentable agent was used in all five cases treated withargon plasma coagulation for post-radiation colitis	**III** Colonic gas explosion is a rare, but potentially serious complication during colonoscopy with electrocautery. Accumulation of colonic combustible gases at potentiallyexplosive concentrations due to poor colon preparation is the cause of gas explosion. Cleansing purgatives (PEG, NaP) that make the bowel safe for electrocautery by decreasing the concentrations of the combustible gases are adequate for colon preparation. Argon plasma coagulationcarries an increased risk of explosion during sigmoidoscopy following enemas, and it should only be performed after full bowel preparation.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE, SCOPUS, SCIRUS, AND EMBASE
	Date restriction	from 1952 to October 2006
	any restriction	Only studies published in English
Selection	Inclusion and exclusion criteria	studies published on colonic gas explosion. Without further specification
Validity assessment	Criteria and process used	Not performed
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	no
Methodological quality	Summary description of results	no
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results descrive narratively

Author, publication year	Study Objective Study Design	Inclusion criteria	Intervention compared	Outcome	Results	Conclusion Level of evidence
Othman 2009	To compare the efficacy of the variable stiffness colonoscope (VSC) with that of the standard adult colonoscope (SAC). Systematic review	Randomised controlled trials comparing the pediatric or adult VSC with the SAC in adults. nonrandomised trials, case reports, and review articles were excluded	Variable stiffness colonoscope Standard adult colonoscope	Caecal intubation rate, caecal intubation time, and ab− dominal pain scores.	**Articles included: 7n. of patients** in each trial ranged from 50 to 467, with a total of 1923 patients (1001− male, 922 female). Mean age ranged from 52 to 63 years. Caecal intubation rate: 8 studies, 1573 participants, OR 2.08 [1.29, 3.36] Caecal intubation time: 7 studies, 1473 participants, WMD −0.21 [− 0.85, 0.43 Abdominal l pain scores during the procedure, 4 studies: SMD = - 0.33, 95% CI ± 0.45 to ± 0.20; in favour of VSC Sedation: VSC was associated with lower doses than SAC of meperidine (WMD= ± 3.76 mg, 95% CI ± 6.91 to ± 0.60; 3 studies) and of midazolam (WMD= ± 0.20 mg, 95% CI ± 0.35 to ± 0.04; 3 studies	I In this metaanalysis we found that use of the VSC showed higher caecal intubation rates, less abdominal pain, and less use of sedation in comparison with the regular adult colonoscope. However, the VSC did not have any distinct advantage over the regular colonoscope in terms of caecal intubation time or the use ofancillary maneuvers. Although the caecal intubation rates were higher with the VSC, it is unlikely that this advantage translates into a distinct clinically meaningful benefit in the hands of experienced colonoscopists, as the difference in the rates is small. However, the VSC could be useful for unsedated colonoscopy in clinical practice. Further studies are needed toaddress the role of the VSC among inexperienced colonoscopists, and in patient populations where colonoscopy is technically difficult.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE COCHRANE LIBRARY, AND ABSTRACTS OF GASTROENTEROLOGY SCIENTIFIC MEETINGS
	Date restriction	Up to February 2008
	any restriction	No restriction
Selection	Inclusion and exclusion criteria	randomised controlled trials comparing the pediatric or adult VSC with the SAC in adults. nonrandomised trials, case reports, and review articles were excluded
Validity assessment	Criteria and process used	Quality assessment performed using validated criteria
Data abstraction	Process used	Data extraction performed by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	a fixed effect model with the Mantel±Haenszel method for pooling dichotomous and continuous data was used. Treatment effects for dichotomous and continuous data outcomes were expressed as odds risks, risk differences, weighted mean differences (WMDs), or standardized mean differences (SMDs). the heterogeneity of trial results was assessed by calculating the I2 measure of inconsistency with a cut off point of I2 = 50%.
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	yes

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Parra Blanco 2006	To compare the cleansing quality of polyethylene glycol electrolyte solution and sodium phosphate with different schedules of administration, and to evaluate whether the timing of the administration of bowel preparation affects the detection of polyps **RCT**	177 consecutive outpatients, aged between 18 and 85 years, scheduled for elective colonoscopy with morning or afternoon appointments	**Group1**: PEG-ELS (Solución Evacuante Bohm, Laboratorios Bohm S.A, Fuenlabrada, Madrid, Spain) 3 Liters starting at 06:00 the same day of colonoscopy ($n = 43$); **Group 2**: NaP (Fosfosoda, Casen Fleet, Utebo, Zaragoza, Spain) 45 mL the day before (20:00) and 45 mL at 06:00 the same day of colonoscopy ($n = 45$); **Group 3**: PEG-ELS 3 L starting at 20:00 the day before ($n = 45$); **Group 4**: NaP 45 mL at 15:00 and 20:00 the day before colonoscopy ($n = 44$).	**Acceptability by patients** (willingness to take the same regimen again if needed) **Bowel cleansing**	**Acceptability by patients** There was no difference regarding the occurrence of nausea, vomiting, thirst, abdominal pain or anal pain among patients in the four groups. A similar proportion of the patients in the different groups rated the preparation as moderately to very disgusting. **Bowel cleansing** Score >4 Group 1: 78.6% ± 0.2 %, Group 2 80.0% ± 0.2%, Group 3 26.7% ± 0.2%, Group 4 6.8% ± 0.1% Groups receiving preparation the same day had significantly better global scores ($P <0.001$) than groups prepared the previous day	**II** The quality of colonic cleansing and the detection of flat lesions are significantly improved when the preparation is taken on the day of the colonoscopy

Quality assessment: adequate sequence generation: yes; adequate allocation concealment: no: blinding of participants and providers: not possible; blinding of outcome assessor: yes; intention to treat analysis or few and balanced lost at follow up: no drop out from the study

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Pellise 2008	to compare the performance of colonoscopy using a high-definition, wide-angle endoscope (HDE) versus a standard colonoscope (SC) for the detection of colorectal neoplasia. RCT	693 consecutive consenting adult patients (age >18) referred from primary care centers for outpatient colonoscopy Patients were excluded if they had polyposis syndromes or hereditary nonpolyposis CRC, previous surgical resection of the colon or rectum, or inflammatory bowel disease. 630 patients completed the stdy	Group 1: HD colonoscopy (n.310) Group 2: SD colonoscopy (n:310)	Acceptability by patients (willingness to take the same regimen again if needed) Adherence to regimen Bowel cleansing	No. of polyps per patient SD: 0.84 ±1.59 HD 0.83 ± 1.30 P: NS . No. of adenomas per patient SD: 0.45 ±1.07 HD 0.43± 0.87 P: NS . No. of adenomas <5 mm per Patient SD: 0.22±0.71 HD 0.28 ± 0.78 P: NS . No. of purely flat adenomas per patient SD: 0.30±0.91 HD 0.21 ± 0.63 P: NS No. of hyperplastic polyps per patient SD: 0.16±0.50 HD 0.18 ± 0.54 P: NS Patients with ≥1 polyp (%) SD: 38% HD: 43% P: NS Patients with ≥1 adenoma SD: 25% HD: 26% P:NS Patients with ≥3 adenomas SD: 5%; HD: 3% P:NS Patients with ≥1 hyperplastic polyp (%) SD: 12%; HD: 13P:NS Patients with HGD adenoma or carcinoma (%) SD: 4%; HD: 4% P:NS	II HDE did not detect significantly more colorectal neoplasia than SC.

Quality assessment: adequate sequence generation: not reported; adequate allocation concealment: not reported; blinding of participants and providers: not possible; blinding of outcome assessor: not possible; intention to treat analysis or few and balanced lost at follow up: 73 patients had to be excluded from further analysis owing to insufficient bowel preparation that precluded satisfactory examination; 620 patients completed the study protocol (HDE, 310 patients; SC, 310 patients).

Author, publication year	Condition	Study Objective Study Design	Participants	Follow up	Outcome	Results	Conclusion Level of evidence
Rabeneck 2008	Patients who who underwent an outpatient colonoscopy during April 1, 2002, to March 31, 2003, in British Columbia, Alberta, Ontario, and Nova Scotia, Canada.	to evaluate the rates of bleeding, perforation, and death associated with outpatient colonoscopy and their risk factors in a population-based study Retrospective population based cohort study	97,091 persons age 50 to 75 years who had an outpatient colonoscopy	30 days	Colonoscopy related deaths Colonoscopy related bleeding Colonoscopy related perforation Patients risk factors for death, bleeding, perforation: age, sex, comorbidity and having a polypectomy performed during the procedure Endoscopist factor: specialisation and experience Assessed by multivariate analysis	**Colonoscopy related bleeding**: 1.64/1000 **Colonoscopy related perforation**: 0.85/1000 **Colonoscopy related deaths**: 0.074/1000 Risk factors: OR (95%CI) **Age (y)** 50–59 1.00 60–75 1.69 (1.18–2.42) **Sex** Male 1.00 Female 0.61 (0.43–0.87) . **Comorbidity score** <3 1.00 >3 0.82 (0.26–2.55) . **Polypectomy** No 1.00 Yes 7.59 (5.07–11.36) **Endoscopist specialty** Gastroenterologist 1.00 General surgeon 0.71 (0.45–1.12) Internist 0.69 (0.4–1.19) .18 FP/GP/Other 0.22 (0.03–1.72) **Endoscopist experience** (quintile #, median, range) #1 63 (1–141) 2.96 (1.57–5.61) #2 178 (142–209) 1.85 (0.98–3.5) #3 248 (210–283) 2.32 (1.25–4.3) . #4 321 (284–378) 1.13 (0.56–2.29) #5 417 (379–1,225) 1.00 **Colonoscopy Setting** Hospital 1.00 Private office or clinic 0.98 (0.53–1.82) .94	**III** Older age, male sex, having a polypectomy, and having the procedure done by a low-volume procedure endoscopist were independently associated with colonoscopy-related bleeding and perforation.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non-exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage. None lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Rex D.K, 2000a	To determine whether colonoscopic withdrawal technique varies between 2 colonoscopists with known differences in adenoma detection rates. Case series Indiana	Ten consecutive colonoscopic withdrawals by each of the 2 (one with the lower miss rate, other with the higher miss rate) colonoscopists were videotaped and then assessed according to specific criteria by 4 experts blinded to who had performed the colonoscopies.	Colonoscopic withdrawals	Features of colonoscope withdrawal evaluated with a score ranging from 0 to 5: adequacy of examination of the proximal side of haustral folds, flexures, rectal valves, and the ileocaecal valve; adequacy of removal of fluid and feces; adequacy of luminal distention; adequacy of time spent viewing.	**Quality scores for colonoscopic withdrawal by colonoscopist with differences in miss rate (**means for all colonoscopies and for all 4 judges. The highest score possible is 35): **Looking on the proximal sides of folds, valves, etc.** Lower miss rate colonoscopist: 31.5 Higher miss rate colonoscopist: 19.6 *P<0.001* **Adequacy of cleaning** Lower miss rate colonoscopist: 33.1 Higher miss rate colonoscopist: 21.9 *P<0.001* **Adequacy of distention** Lower miss rate colonoscopist: 33.5 Higher miss rate colonoscopist: 24.0 *P<0.001* **Adequacy of time spent viewing** Lower miss rate colonoscopist: 32.4 Higher miss rate colonoscopist: 21.0 *P<0.001* **Mean withdrawal time** Lower miss rate colonoscopist: 8 minutes, 55 seconds Higher miss rate colonoscopist: 6minutes, 41 seconds *P=0.02*	V Higher quality colonoscopic withdrawal technique as determined by expert observers was associated with a colonoscopist with a previously documented lower miss rate for adenomas. Colonoscopic withdrawal technique should be subjected to further study and standards for withdrawal technique should be developed.

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
Rostom 2006	To compare the efficacy, safety, and tolerability of different regimens of oral NaP and polyethylene glycol (PEG). **RCT**	193 patients between the age of 18 and 80 years referred for colonoscopy at The Ottawa Hospital; mean age 48 years	Group (1) oral NaP, 2 bottles (45 mL each) 6 hours apart; Group (2) oral NaP, 2 bottles 12 hours apart; (Group 3) oral NaP, 2 bottles 24 hours apart; Group (4) 4 L PEG	**Acceptability by patients** (willingness to take the same regimen again if needed) **Bowel cleansing**	**Acceptability by patients** the various bowel preparations were generally not well tolerated by patients. 65% to 82% of patients in the studied groups had moderate or great difficulty drinking the preparation (no significant group differences). There was a nonsignificant trend toward fewer patients being able to complete the PEG preparation than the oral NaP preparations, and significantly more people would refuse PEG if offered again compared with the oral NaP groups (p Z 0.010). Significantly fewer people would refuse the 24-hour NaP preparation than the other oral NaP regimens (p Z 0.044). **Bowel cleansing** Total mean score Group 1: 3.26 Group 2 2.25 Group 3 2.18 Group 4 3.17	**II** A 24- or 12-hour NaP bowel preparation strategy was more effective than NaP 6 hours apart or PEG. PEG use is associated with more residual colonic fluid but represents an alternative to NaP in some clinical situations.

Quality assessment: adequate sequence generation: yes; adequate allocation concealment: yes; blinding of participants and providers: not possible; blinding of outcome assessor: yes; intention to treat analysis or few and balanced lost at follow up : no drop out from the study.

Author, publication year	Condition	Study Objective Study Design	Participants	Follow up	Outcome	Results	Conclusion Level of evidence
Singh 2009	All adults (>16 years) individuals who had an admission within 30 days of the initial outpatient lower GI endoscopy to one of the hospitals in Winnipeg. between April 1, 2004, and March 31, 2006, **Canada.**	To evaluate the current practice of lower GI endoscopy, focusing on the reporting and colonoscopy completion rates, and to determine the rates of lower GI endoscopy–associated complications in the usual clinical practice retrospective chart audit	24,509 outpatient lower GI endoscopies The mean (SD) age of individuals undergoing the procedures was 59 ±15 years, and 56% were women.	30 days	Frequency of complications Endoscopist factor: specialisation and experience	**bleeding**: 0.86/1000 **perforation**: 1.18/1000 complication rate among procedures performed at **teaching hospitals vs community hospitals** : (19/6186 vs 50/18,323, P: NS) complication rate among the endoscopists of different specialties (general surgeons 41/13,705, gastroenterologists 23/9618, family physicians 5/1180; P:NS). There was a linear trend for a decreasing rate of complications for endoscopists performing a higher number of procedures (P <.02 for trends). The complication rate for those performing less than 200 per year was twice that for the rest (13/2400 or 5.4/1000 vs 55/ 20,365 or 2.7/1000. P <.02, relative risk 2 [95% CI, 1.1-3.7]).	**III** A higher complication rate after endoscopy by low-volume endoscopists have been reported but needs to be further evaluated.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non-exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record (eg clinical records); adjustment for multiple prognostic factor confounding :no. Assessment of outcomes by record linkage. None lost at follow up.

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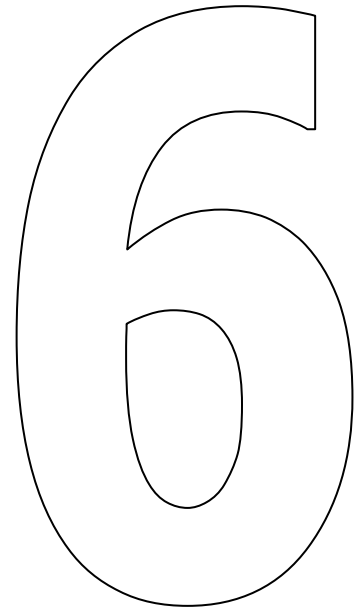
Professional requirements and training
EVIDENCE

EU CRC Guidelines Literature Group

6.1 Professional and training requirements for colorectal cancer screening

6.1.1 Summary document

Rita Banzi

SEARCH METHOD

We searched MedLine, CENTRAL, and The Cochrane Library using the following search strategy: ("Mass Screening"[MeSH Major Topic] OR screen*) AND ("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND "Education"[Mesh] OR (professional training OR professional requirement*)

CLINICAL QUESTION 1

What are the professional and training requirements for primary care physicians?

PICOS

P: Primary care physicians
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Optimal uptake of colorectal screening (screening compliance)
S: Observational studies RCTs, systematic reviews

RESULTS

We found three RCTs (1-3), one pre-test post-test study (4), and one cross-sectional study (5) addressing this issue.

In an American RCT, 8 health centers (63 physicians) of adult primary care services were randomised to educational intervention on CRC (epidemiology and risk assessment, guidelines and methods, behavioural approaches to improving patient CRC screening, theories of health behaviour, barriers to screening, risk communication, informed and shared decision-making) or to a control group. This intervention improved CRC screening rate (AdjOR=2.25 (95% CI 1.67–3.04), p<0.001) (1).

The trial by Walsh et al. assessed the effect of an intervention targeting physicians and their patients on rates of CRC screening (FOBT) in a US community setting. 94 community primary care physicians were randomly assigned to a control group or to an intervention group receiving an educational seminar and ''academic detailing'' (2). 9 652 patients were enrolled for 2 years, and 3 732 patients were enrolled for 5 years. There was no increase in any CRC screening that occurred in the intervention group for patients enrolled for 2 years and 5 years (12.7 increase vs. 12.5%, p=0.51; 9.7% increase vs. 8.6%, p=0.45). The third RCT was performed on health care providers in a primary

care setting: the intervention consisted in a 2-hour workshop on rationale and guidelines for CRC screening and on improving communication with patients with low literacy skills. Every 4 to 6 months, providers were invited to attend 1-hour feedback sessions, during which they received information on the firm's CRC screening recommendation rate, individualized confidential feedback, and patient compliance with recommended tests (3). A statistically significant improvement in % of eligible patients who received provider recommendations for colorectal cancer screening and thepercentage of eligible patients who completed a colorectal cancer screening test (home FOBT, flexible sigmoidoscopy-FS, or colonoscopy-COL) in the intervention group vs. no intervention was found.

We also found one pre test-post test study (4) and one cross-sectional study (5) which confirmed an improvement in screening rate following a facilitator intervention with screening recommendation and flexible sigmoidoscopy training.

CONCLUSIONS

From evidence derived from two good quality RCTs it appears that educational programmes on CRC screening rationale, recommendation, CRC risk, etc. for primary care physicians are effective in improving CRC screening rates. However, a third RCT did not confirm these results (LEVEL OF EVIDENCE II).

CLINICAL QUESTION 2

What are the professional and training requirements for endoscopists?

PICOS

P: Endoscopists
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Safe, tolerable, and accurate diagnostic procedure. Complete and safe endoscopic resection
S: Observational studies

RESULTS

We found three studies assessing whether specific professional and training requirements for endoscopists affect the efficacy, safety, tolerability, and accuracy of endoscopic procedures (6-8). One retrospective database review examined 5 477 consecutive colonoscopies performed by 10 gastroenterologists over a 6-year period to determine the rate and documentation of caecal intubation, an important measure of competence (6). This study reported an overall adjusted caecal intubation rate for the entire 6 years of 90.3%, with a highest adjusted rate (93.7%) in the most recent year studied. Although data were not reported, this review also found no correlation between endoscopist experience and number of procedures/year and caecal intubation rate.

A UK study performed on 13 medical endoscopists who each performed about 3000 flexible sigmoidoscopies (200 per month) using the same equipment and protocol investigated whether the observed differences in adenoma detection rate (ADR) among gastroenterologists could be attributed to varying performance by endoscopists (7). ADR varied between 15.9% and 8.6% with a statistically significant difference between endoscopists (χ^2=204.8; p<0.0001; coefficient of variation, 20.3%). There was also a highly significant variation between endoscopists in the detection rates of polyps of all types and of large (>1 cm) polyps. These differences in ADRs were not explained by patient characteristics, incidence of colorectal cancer in the local population, or the endoscopists' medical specialty or previous experience. Average ADRs increased significantly with screening experience (up to 400 examinations). Finally, a small cross-sectional study performed in the UK on 21 doctors generally reported that accelerated teaching of skills in colonoscopy can deliver long-term benefit. If

this approach were widely adopted, it could have a significant impact in securing quality colonoscopy services (8).

CONCLUSIONS

Only a few data from low-quality studies were retrieved on this issue. Thus, it is difficult to conclude which professional and training requirements for endoscopists may affect the efficacy, safety, tolerability, and accuracy of endoscopic procedures (LEVEL OF EVIDENCE V).

CLINICAL QUESTION 3

What are the professional and training requirements for radiologists?

PICOS

P: Radiologists
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Accurate radiological assessment of the large bowel
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for radiologists to improve accurate radiological assessment of the large bowel in a CRC screening programme.

CLINICAL QUESTION 4

What are the professional and training requirements for pathologists?

PICOS

P: Pathologists
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Accurate and reproducible diagnosis and staging
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for pathologists to reduce operative morbidity and mortality following CRC screening programmes

CLINICAL QUESTION 5

What are the professional and training requirements for surgeons?

PICOS

P: Surgeons
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Low operative morbidity and mortality. High long-term cancer specific survival
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for surgeons to reduce operative morbidity and mortality following CRC screening programmes.

CLINICAL QUESTION 6

What are the professional and training requirements for laboratory staff?

PICOS

P: Laboratory staff
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Accurate interpretation of the chosen faecal occult blood test
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for laboratory staff to improve the accuracy of FOBT results.

CLINICAL QUESTION 7

What are the professional and training requirements for administrative and clerical staff?

PICOS

P: Administrative and clerical staff
I: Educational and training interventions
C: No intervention; different kind of intervention

O: An efficient colorectal screening programme
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for administrative and clerical staff to improve CRC screening efficacy.

CLINICAL QUESTION 8

What are the professional and training requirements for nurses?

PICOS

P: Nurses
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Good communication with screen positive individual, high quality endoscopy studies
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for nurses to improve communication and endoscopy quality in CRC screening programmes.

CLINICAL QUESTION 9

What are the professional and training requirements for public health specialists?

PICOS

P: Public health specialists
I: Educational and training interventions
C: No intervention; different kind of intervention
O: Appropriate and efficient screening programmes
S: Observational studies

RESULTS

We found no studies on this issue.

CONCLUSIONS

We found no evidence on the impact of professional and training requirements for public health specialists to improve CRC screening efficacy.

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6.1.2 Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Lane 2008	RCT	To assess provider if interventions within health center practices could improve the delivery/utilisation of CRC screening	8 health centers 63 physicians and physician extenders deliver adult primary care services at the health centers, 31 in the intervention centers and 32 in the control centers chart audit: 2224 patient survey: 281 USA	***Intervention centres:*** Pre-intervention: the educator/facilitator met with the Medical Director and Administrator of each health center 1 hour evidence-based clinician education intervention (CRC epidemiology and risk assessment, guidelines and methods, Behavioural approaches to improving patient CRC screening-theories of health behaviour, barriers to screening, risk communication, informed and shared decision-making) ***Control Centres*** Pre-intervention and training on obesity	CRC screening defined as referral for screening sigmoidoscopy or colonoscopy, or dispensing of an FOBT kit, and/or completion of CRC screening. Post intervention patient survey	***Pre- to post-intervention changes in CRC screening*** Intervention group: 45% vs. 61%, *p*<0.001 Control group: 37% vs. 41%, *p*=0.40 AdjOR=2.25 (95% CI 1.67–3.04), *p*<0.001 ***Proportion of patients reporting agreement that they needed more advice and information to make good decisions about CRC screening*** (pre vs. post intervention) Intervention group: 50% vs. 24%, p=0.006 Control group: 69% vs. 63%, p=0.27	**II** This study demonstrated the feasibility of conducting a CRC educational activity in conjunction with a system directed non-educational intervention for providers who serve disadvantaged populations, resulting in increased compliance with CRC screening. Moreover, a statistically significant decrease in intervention versus control patient reports of the need for more advice and information for CRC screening decision-making was found.

Quality assessment: protection against selection bias and contamination: cluster randomisation to determine the intervention and control groups; protection against detection bias: screening rate was assessed by chart audits of the 1 year period before and after the intervention (no info on blinded assessment). Adjustment for cluster level (health center, baseline screening rates, proportion of health center registrants aged 50 and older, ratio of providers/100 patients) and individual-level covariates (age, gender, race/ethnicity; medical insurance).

Author	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Walsh 2005	To assess the effect of an intervention targeting physicians and their patients on rates of CRC screening RCT	Recommended screening: annual FOBT and SIG every 5 years or COL every 10 years Intervention: physician component: educational seminars and "academic detailing" All physicians enrolled in the study received a summary of the presentation regardless of whether they attended the seminars; patient component: personalized letter, an educational brochure, and an FOBT kit with instructions for completion, and a stamped return envelope Control: usual care	94 physicians (2/3 male, the majority of physicians practiced in a community setting and individually) randomised to the intervention and control groups 7993 patient (mean age 64 year old) enrolled from all patients aged 50 to 79 years who were not up-to-date with CRC screening were identified. Setting: primary care (family practice or internal medicine physicians recruited from a large individual practitioner association, IPA) USA	1 year	patient screening rates physicians screening rates Physician screening rates were calculated as the number of a physician's patients who underwent screening divided by the number of patients eligible for screening	***Increase from Baseline in CRC Rates Among Patients Continuously Enrolled for 2 and 5 years*** FOBT (pts continuously enrolled for 2 years) Control: 13.1%; Intervention: 11.4%; p=0.05 Any test (pts continuously enrolled for 2 years) Control: 12.5%; Intervention: 12.7%; p=0.51 SIG (pts continuously enrolled for 5 years) Control: 4.4%; Intervention: 7.4%; P<0.01 Colonoscopy (pts continuously enrolled for 5 years) Control: 8.9%; Intervention: 9.5%; p=0.46 Any test (pts continuously enrolled for 5 years) Control: 8.6%; Intervention: 9.7%; p=0.45 ***Mean Change (standard error) Physician Screening Rates Pre- and Post-Intervention for Patients Continuously Enrolled for 2 and 5 years*** FOBT (pts continuously enrolled for 2 years) Control (N=44): 15.9 (0.02); Intervention (N=50): 12.7 (1.9); p=0.25 Any test (pts continuously enrolled for 2 years) Control (N=44): 13.7 (1.0); Intervention (N=50): 12.6 (1.0); p=0.47 SIG (pts continuously enrolled for 5 years) Control (N=38): 7.7 (2.3); Intervention (N=44): 6.1 (2.2); p=0.61 Colonoscopy (pts continuously enrolled for 5 years) Control (N=38): 7.5 (2.2); Intervention (N=44): 10.6 (2.1); p=0.32	**II** This combined intervention on physicians about CRC screening resulted in a modest increase in SIG but no effect on other screening outcomes: there was a greater increase in the percentage of patients in the intervention group who had a FOBT and a SIG at follow-up when compared with the control group.

Author	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Any test (pts continuously enrolled for 5 years) Control (N=38): 9.3 (2.0); Intervention (N=44): 9.7 (1.9); p=0.91	

Quality assessment: physicians were the unit of randomisation and analysis; block randomisation, stratified by group size (adequate protection of contamination), unclear allocation concealment; double blinding: not relevant; lost at follow up.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Ferreira 2005	RCT	To test whether a health care provider–directed intervention increased CRC screening rates	Health care providers in the two participating firms: Control group: 3 attendings, 1 nurse practitioner, a total of 49 residents Intervention group: 3 attendings, 2 nurse practitioners, a total of 55 residents Patients: 1978 male veterans 50 years and older General medicine primary care outpatient firm Veteran Medical Center May 2001 to June 2003 USA	*Intervention centre:* 2 months before the initiation of the study: a 2-hour workshop on rationale and guidelines for CRC screening and on improving communication with patients with low literacy skills. Every 4 to 6 months, providers were invited to attend 1-hour feedback sessions, during which they received information on the firm's CRC screening recommendation rate, individualized confidential feedback, and patient compliance with recommended tests. *Control Centre:* No information	% of eligible patients who received provider Recommend-ations for colorectal cancer screening and percentage of eligible patients who completed a colorectal cancer screening test (home FOBT, flexible sigmoidoscopy-FS, or colonoscopy-COL).	***Screening Recommended*** <u>Intervention group (N=1015):</u> Any screening: 76.0 % FOBT only: 6.3% FS/COL only: 19.2% FOBT and FS/COL: 50.4 % <u>Control group (N= 963):</u> Any screening: 69.4% FOBT only: 2.8% FS/COL only: 44.4% FOBT and FS/COL: 22.1% p value (Any screening)=0.02 ***Completion of the screening*** <u>Intervention group (N=1015):</u> Any screening: 41.3% FOBT only: 22.6% FS/COL only: 12.2% FOBT and FS/COL: 6.5% <u>Control group (N= 963):</u> Any screening: 32.4% FOBT only: 14.3% FS/COL only: 15.3% FOBT and FS/COL: 2.8% p value (Any screening)=0.003	**II** A health care provider– directed intervention that provided feedback on individual and firm-specific colorectal cancer screening recommendation and compliance rates resulted in a 7% absolute increase in the rates of CRC screening recommendations documented by providers in electronic medical records and a 9% absolute increase in the rates of completion of colorectal cancer screening (by FOBT, FS or COL).

Quality assessment: protection against selection bias and contamination: cluster randomisation (no info on sequence generation and allocation); protection against detection bias: screening rate was assessed by a medical record analysis (no info on blinded assessment).

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
Wei 2005	Pre test post test uncontrolled study	To test the feasibility and effect of having facilitators help primary care practices implement office systems to improve CRC screening behaviour	1972 internal medicine and family practice clinicians were invited 276 (14.0%) answered the invite, 185 were enrolled in the study 127 (87.6%) completed their questionnaire New Hampshire, Massachusetts, and Connecticut USA	Facilitator intervention* to improve CRC screening behaviour (educating patients, identifying patients due for screening, enabling patient compliance, monitoring patient compliance, and notifying patients of their test results) *assessment contact (during which the facilitator introduced the intervention and asked each clinician to complete the baseline questionnaire), a planning visit (during which the facilitators met with enrolled clinicians and staff to discuss their current screening process, offer suggestions, introduce the tool kit, and reflect on ways to improve their screening process), and 1or more reinforcement follow-ups (during which the facilitators provided an opportunity for clinicians to order more materials, reinforced any changes already made, and addressed any barriers that the providers had encountered).	6 months (Approximately 6 months after the planning visit, the facilitators made a final evaluation visit, when the follow-up questionnaire was administered or left for self-administration)	Number of clinicians reporting each CRC screening behaviour Medical record audit individual clinician as the unit of observation	***Educating patients about colorectal cancer Screening (%)*** <u>Posters or brochures in the examination or waiting rooms</u> Baseline: 26 (20.5); FU: 88 (69.3); p<0.001 <u>Brochures actively distributed to patients</u> Baseline: 19 (15.0); FU: 55 (43.3); p<0.001 <u>Clinicians discuss screening</u> Baseline: 122 (96.1); FU: 121 (95.3) <u>Staff discuss screening</u> Baseline: 26 (20.5); FU: 46 (36.2); p<0.05 ***Identifying patients who are due for screening (%)*** <u>None</u> Baseline: 10 (7.9); FU: 3 (2.4) <u>Health maintenance flow sheet</u> Baseline: 86 (67.7); FU: 79 (62.2) <u>Computer prompt</u> Baseline: 6 (4.7); FU: 11 (8.7) <u>Medical record identifier</u> Baseline: 4 (3.1); FU: 14 (11.0); p<0.05 <u>Notation in progress note</u> Baseline: 82 (64.6); FU: 77 (60.6) **Subset of those who recommended FOBT at baseline and follow-up (n = 102)**	**V** A significant improvement in the category of patient education (p<0.001) and in the combined category of enabling and monitoring FOBT (p=0.008) has been demonstrated However this trial has design weakness (no control) which can have affect results The conclusion should be regarded with caution because of the weaknesses of the study: no ctrl group, no adjustment for trend

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
							Enabling and monitoring patient compliance Written FOBT instructions Baseline: 85 (83.3); FU: 88 (86.3) Return envelopes Baseline: 93 (91.2); FU: 93 (91.2) Recorded date when FOBT kits were provided Baseline: 78 (76.5); FU: 87 (85.3) Monitor patient compliance using a computer Baseline: 2 (2.0); FU: 5 (4.9) Monitor patient compliance using a manual system Baseline: 21 (20.6); FU: 38 (37.3); p<0.05 Do not monitor Baseline: 75 (73.5); FU: 49 (48.0) p<0.001 Missing response Baseline: 4 (3.9); FU: 1 (1.0) ***Notifying patients of normal test results*** Not notified Baseline: 24 (23.5); FU: 23 (22.5) Postcard or letter Baseline: 47 (46.1); FU: 52 (51.0); p<0.05 Telephone call Baseline: 33 (32.4); FU: 27 (26.5) ***Notifying patients of abnormal test results*** Postcard or letter Baseline: 19 (18.6); FU: 18 (17.6) Telephone call Baseline: 94 (92.2); FU: 92 (90.2)	

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Lewis 2000	Cross-sectional study	To assess the impact of flexible sigmoidoscopy training on compliance with current screening recommendations	232 patients, 68 physicians Stratified random sample of 7 patients for physician extracted from all patients aged 50 to 75 years as of January 1, 1997, identified by the database of the University of Pennsylvania excluding those with specific co morbidities USA	Different physician training	Rates of screening for colorectal cancer and rates of undergoing flexible sigmoidoscopy across patient groups according to the physician's training	***Physicians trained to perform flexible sigmoidoscopy*** 38/68 (56%) ***Physicians reporting interest in obtaining training*** 12/68 (18%) ***Comparison of compliance with screening recommendations according to Primary Care Physician Training (yes or No)*** <u>Any colorectal cancer screening</u> OR 1.16 (0.67-2.01) <u>FS</u> OR 2.26 (0.78-6.57) <u>Faecal occult blood testing</u> OR 1.03 (0.56-1.91)	V the overall rate of colorectal cancer screening does not differ between patients cared for by physicians who are or are not trained to perform flexible sigmoidoscopy.

Quality assessment: Selection bias could be distorting the results: Physicians who choose to be trained in flexible sigmoidoscopy and who choose to perform this procedure in their practice might differ from other physicians. Physicians who believe strongly in the role of preventive medicine could be more likely to seek training in flexible sigmoidoscopy. This group would then be expected to emphasize more strongly the need for colorectal cancer screening and particularly the need for flexible sigmoidoscopy.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Aslinia 2006	Cross-sectional study	To determine overall and individual endoscopist caecal intubation rates for a 6-yr interval and to compare these results to recommended thresholds set by the MSTF and ASGE; (2) to identify trends in the rate of caecal intubation; (3) to identify circumstances associated with successful caecal intubation; (4) to evaluate the quality of written and photographic documentation of caecal intubation; (5) to use this information	5,477 consecutive colonoscopies performed by 10 gastroenterologists over a 6 years period. University of Maryland Medical Center USA	Colonoscopy	Trends in overall and individual caecal intubation rates, circumstances that impact these rates quality of documentation of caecal intubation	***Overall adjusted caecal intubation rate (6 yr period)*** 90.3% 9/10 endoscopists who performed procedures analysed in this study had unadjusted caecal intubation rates that ranged from 88% to 97% (mean=95%). Individual caecal intubation rates did not correlate with either the mean years of endoscopic experience or the mean number of procedures performed/year (data supporting this statement not shown).	V In this university-based unselected patient population, male gender, adequate bowel preparation, and procedures performed on outpatients for colon cancer screening predicted a higher caecal intubation rate

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Atkin 2004	Cross-sectional study	To determine whether the observed differences in adenoma detection rate among gastroenterologists could be attributed to varying performance by endoscopists, to examine the effect of experience on performance	Data on 38,601 patients of 40,674 involved in the UK Flexible sigmoidoscopy Screening trial Mean age 60.5 yrs (SD 2.89) who received FS by 13 endoscopists (one for each centre) UK	Flexible sigmoidoscopy	Adenoma detection rate (ADR) Factor predictive of variation of the ADR assessed by multivariate logistic regression	*Overall ADR* 12.1% Rates varied between 15.9% and 8.6%, statistically significant difference between endoscopists (χ^2=204.8; *p*<0.0001; coefficient of variation, 20.3%) statistically significant variation between endoscopists in the detection rates of polyps all types χ^2=913; *p*<0.0001; coefficient of variation, 26.2% large (>1 cm) polyps χ^2=45.7; *p*<0.0001; coefficient of variation, 22.6% ADRs correlated with detection rates of nonadenomatous polyps (0.57, p=0.04) The variation in ADRs was not due to differences in the medical specialty of the endoscopist (surgeon or gastroenterologist), the incidence rate of CRC in the population living in the catchment area of the center, or previous endoscopic experience as shown by multivariate logistic regression using ADR as outcome	V Differences in ADRs were not explained by patient characteristics, incidence of colorectal cancer in the local population, or the endoscopists' medical specialty or previous experience. Average ADRs increased significantly with screening experience (up to 400 examinations).

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
Thomas Gibson 2007	Before after un-controlled study	To assess the efficacy of a novel, intensive course in colon-oscopy (Accelerated Colon-oscopy Training Week-ACTW) and to establish whether any improvement in skills seen following accelerated training was sustained beyond 6 months	Twenty-one doctors (trainees) training in colorectal surgery (n = 12) and gastro-enterology (n = 9)

UK | ACTW: Day 1: Assessments & live case training Days 2 & 3: Simulator & and live case training Day 4: Live case training & assessments Day 5: Simulator training & assessment | Three time points: Pre-training assess-ments Post-training assess-ments Assess-ments at 6 month FU | Knowledge (MCQ and Simulator test cases: total procedure time, insertion time, extubation time, percentage of time spent in red-out, the percentage of mucosa visualized, and the efficiency ratio)

Skills (Direct Observation of Procedural Skill DOPS) (i) general approach to the patients, staff, and procedure, including consent and sedation; (ii) basic technique, correct use of right and left hands; (iii) understanding of looping and use of ancillary manoeuvres; (iv) caecal identification and intubation/ileal intubation; (v) withdrawal technique; (vi) basic therapy: hot biopsy, polypectomy Tri-split video assessment 1: "Not competent, needs full supervision"; 2: "Reasonably competent, capable of performing colonoscopy but may require some supervision"; 3: "Fully competent, capable of performing unassisted colonoscopy" | *Knowledge* MCQ score (SD) Pre-training: 57.2% (11.8) Post training: 67.8% (7.2) $p < 0.001$ Follow up: 65.9% (8.2) $p = 0.06$ (vs. post training) Simulator no significant change in any of the other parameters recorded by the simulator; none of the 16 trainees who returned for follow-up had used a simulator in the intervening period *Skills* Direct Observation of Procedural Skill Both trainers recorded a significantly higher global grade following training; No significant change in any of the performance parameter scores at follow-up assessment compared to post-training Tri-split video assessment Scorer 1 found a significant increase in the global grade after training while for the scorer 2 did not reach significance; No significant change in any of the individual parameters nor the global grade at follow-up compared to immediately post training | V

This study demonstrates that accelerated skills teaching in colonoscopy can deliver long-term benefit. If this approach were widely adopted, it could have a significant impact in securing quality colonoscopy services. |

Quality assessment: Two experienced endoscopists independently scored cases from all 21 trainees at the three different time points. Cases were randomised; the trainee, trainer, and training time point were unidentifiable from the video footage.

6.2 Additional evidence tables prepared after December 2009

1. Morris M & Platell CF (2007), Surgical volume influences survival in patients undergoing resections for stage II colon cancers, *ANZ.J.Surg.*, vol. 77, no. 10, pp. 902-906.

2. Salz T & Sandler RS (2008), The effect of hospital and surgeon volume on outcomes for rectal cancer surgery, *Clin.Gastroenterol.Hepatol.*, vol. 6, no. 11, pp. 1185-1193.

Author, publication year	Study Objective Study Design	intervention	Participants	Outcomes	Results	Conclusion Level of evidence
Morris M., 2007	To determine whether surgical volume was an independent predictor for overall and cancer-specific survival in patients undergoing surgery for stage II colon cancer. Retrospective population-based study Australia	Resection for stage II colon cancers	1,467 patients underwent resection for stage II colon cancer between 1993 and 2003. Pathology records from four hospital pathology departments in the State of Western Australia.	Overall survival, lymph nodes per specimens, adjuvant chemotherapy, proportion of obstructed and perforated, percentage of poor prognosis cancer, 30 day mortality,	106 surgeon who carried out these 1467 resection. **Distribution of resection carried out by surgical volume, N** ≤10=270 10-25=420 >25=493 unknown=284 **Lymph nodes per specimens by surgical volume, *p(between the groups)*** ≤10=11±8 10-25=12±8 >25=13±7 unknown=11±8 *p*=0.002 **Adjuvant chemotherapy(%), *p(between the groups)* by surgical volume** ≤10=10 10-25=9 >25=15 unknown=9 *p*=0.018 **30 day mortality (%), *p(between the groups)* by surgical volume** ≤10=3.7 10-25=4.0 >25=3.7 unknown=6.0 *p*=ns **Poor prognosis (T3 cancer with vascular invasion or T4 cancer with or without vascular invasion) by surgical volume (%), *p(between the groups)*** ≤10=33 10-25=26	**III** Surgical volume was a significant independent predictor for survival in patients undergoing resections for stage II colon cancers. Surgeons carrying out only 25 procedures over a 10-year period outperformed surgeons doing fewer cases.

					>25=30 unknown=26 *p*=ns **Obstructed (%), *p(between the groups)* by surgical volume** ≤10=18 10-25=18 >25=15 unknown=19 *p*=ns **Perforated (%), *p(between the groups)* by surgical volume** ≤10=9 10-25=9 >25=10 unknown=7 *p*=ns **Overall survivals by surgical volume** ≤10=54.0 (47.9-60.1) 10-25=59.4 (54.7-64.1) >25=72.8 (68.7-76.9) p=0.001 unknown=56.7 (50.8-62.6) **Cox proportional hazard model to examine overall survival; p, HR (95% CI)** Colon resection/decade ≤10= 1.00 10-25=0.054, 0.816 (0.663-1.003) >25=0.0001, 0.657 (0.532-0.811) Other significant predictors: surgery in a private hospital, use of chemotherapy, age at diagnosis and T staging and vascular invasion.	

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
Salz T., 2008	To determine whether hospital and surgeon volume influenced the type of surgery performed and outcomes of surgery for rectal cancer. Systematic review	Rectal cancer surgery	22 studies (N=5984195 patients) from 8 North american and european countries during the years 1979 to 2002. 11 studies on the influence of hospital volume; 6 studies on the influence of surgeon volume and 5 studies addressed on both	Short and long-term surgical outcomes: complication, mortality, survival, and recurrence rates.	**Surgical complication** 1 study reported a relationship between higher surgeon volume and lower complication rate (OR=0.7) **Recurrence risk:** The role of surgeon volume on local recurrence rate was assessed in four studies: -no association in 1 study -higher -volume surgeons had lower local recurrence in 3 studies (HR =0.42 and HR=0.56 in 2 studies and 11% high vs 17% low volume surgeons in the other study) **Mortality** The effect of surgeon volume on postoperative mortality was assessed in six studies: -no effect of surgeon volume in 4 study -higher -volume surgeons had lower mortality rates in 2 studies (OR=0.87 and OR=0.58) **Survival** Overall survival : 2 studies of surgeon volume Only in 1 study significant relationship between higher surgeon volume and longer survival (RR=1.35) Relative survival: 5 studies of surgeon volume Only in 2 studies significant effect of volume and relative survival (HR=1.4, HR=1.89) **Use of adjuvant therapy** No effect of surgeon volume on use of adjuvant therapy	**III** Despite the variation in study design and quality, a clear pattern of the effect of hospital and surgeon volume on rectal cancer treatment and outcomes emerges from this systematic review. Surgeons with higher caseloads appear to have lower postoperative mortality rates. Surgeon volume appear to have no effect or a small beneficial effect on the rate of leaks, complication rates, local recurrence, overall survival, and cancer-specific survival.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE
	Date restriction	Up to april 2007
	any restriction	Only English published studies considered
Selection	Inclusion and exclusion criteria	Studies which include results for rectal cancer patients and that report original data for which bivariate or multivariate results were calculated. Studies reporting results without showing effect sizes were include. Articles for which results for rectal cancer could not be distinguished from larger patient groups, such as articles in which cancers of the colon and rectum were aggregated were excluded
Validity assessment	Criteria and process used	Quality assessment performed using the following criteria: study design (retrospective or prospective), recency of data collection, data source, sample size, and inclusion of important prognostic factors in multivariate analyses.
Data abstraction	Process used	Study selection performed by only one authors; not reported information about data abstraction
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	resutls reported narratively
	summary results	yes

7

Quality assurance in pathology in colorectal cancer screening and diagnosis
EVIDENCE

EU CRC Guidelines Literature Group

7.1 Use of Vienna classification to improve the diagnostic reproducibility of the assessment of colorectal neoplastic lesion

7.1.1 Summary document

Rita Banzi

CLINICAL QUESTION 1

Does the use of the Vienna classification improve the diagnostic reproducibility of assessment of colorectal neoplastic lesions?

PICOS

P: Asymptomatic people detected with polyps
I: Pathological diagnosis using Vienna classification
C: Standard classification – mild, moderate and severe dysplasia, WHO classification
O: Diagnostic reproducibility/concordance
S: (Systematic reviews of) diagnostic accuracy; cross-sectional studies, case series

INTRODUCTION

Gastrointestinal lesions considered to be high-grade adenoma/dysplasia by Western pathologists using the conventional Western classification are often diagnosed as carcinoma by Japanese pathologists using the Japanese group classification. (1) Western pathologists considered invasion into the lamina propria of the mucosa mandatory for the diagnosis of carcinoma, whereas nuclear and structural features were more important for the Japanese.

For these reasons about 30 pathologists from 12 countries met in Vienna and reached a consensus on the terminology for gastrointestinal epithelial neoplasia, the Vienna classification.

At the beginning of 2000, the Vienna classification was revised to include intramucosal carcinoma as a fourth subcategory of category 4, because it is often hard to determine whether or not there is invasion into the lamina propria, and because the distinction between any of the four subcategories is irrelevant from a therapeutic viewpoint.

Table 1   Vienna classification of gastrointestinal epithelial neoplasia

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Non-invasive low grade neoplasia (low grade adenoma/dysplasia)
Category 4	Non-invasive high grade neoplasia
	4.1 High grade adenoma/dysplasia
	4.2 Non-invasive carcinoma (carcinoma in situ)*
	4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia
	5.1 Intramucosal carcinoma†
	5.2 Submucosal carcinoma or beyond

*Non-invasive indicates absence of evident invasion.
†Intramucosal indicates invasion into the lamina propria or muscularis mucosae.

SEARCH METHOD

We contacted experts in the field to retrieve papers relevant to this issue. We also performed a search on <u>MedLine</u> using the following keywords: gastrointestinal neoplasm/classification, colorectal neoplasm, Vienna classification. Additional papers were collected hand-searching the bibliography of relevant studies.

RESULTS

One out of the four papers suggested by the experts was included in the analysis (2). The table of evidence of a narrative review (3) and an editorial paper (4) were not done. However, these papers were considered as a background and in the conclusion of this summary. Lastly, we were not able to retrieve the full text of the fourth publication. (5)

From the analysis of title and abstract, nine out of the 19 citations retrieved from the MedLine search were considered relevant for the issue, but the full text of two of theme was not available.

This summary was finally based on four publications related to the World Congress of Gastroenterology workshop held in Vienna in 1998 (2-4, 6) and a subsequent case-control study (7).

Few data are available regarding the diagnostic reproducibility of the Vienna classification compared to the standard and/or WHO classification of colorectal neoplasia. The extent of agreement between Japanese and Western viewpoints, according to the classification of neoplasia on which the regrouping of diagnoses into categories is based, was discussed during a workshop in Vienna where 31 pathologists from 12 countries individually diagnosed the same 20 colorectal specimens. (2, 6) Pathologists with a Western viewpoint diagnosed suspected or definite carcinoma in 5–40% of the 20 colorectal lesions while pathologists with a Japanese viewpoint diagnosed suspected or definite carcinoma in 45–75% of the colorectal lesions. The percentage of specimens for which there was agreement was 45% (Kappa values: 0.27). When the Vienna Classification and the Vienna Classification revised were used the agreement among pathologists increased to 65% (Kappa value: 0.47) and 70% (Kappa value: 0.54), respectively. Moreover, these studies analysed the therapeutic usefulness of the classification showing that the revised Vienna Classification had fewest mismatches between category numbers and clinical implications (6). For categories 1, 4, and 5, the clinical implications are respectively: no (or optional) follow-up; local resection; and surgery including lymph node dissection. The implication of category 3 of the revised classification is, in part, the same as that of category 2 (follow-up) and in part the same as that of category 4 (local endoscopic resection). The impact of the revised Vienna classification on levels of histological agreement between pathologists was investigated within a case-control study performed on 144 British patients with adenomatous polyps or cancer matched with 144 Japanese patients with adenoma or cancer (n=144) (7). One colonoscopist, extensively trained in the identification of flat colorectal neoplasms, performed all the colonoscopies, and subsequent histological examination of every neoplasm removed at colonoscopy was undertaken by two British as well as two Japanese pathologists. Under the conventional classification, British pathologists tended to agree on their diagnoses more often than Japanese pathologists. Discrepancies in histological diagnoses between pathologists were reduced with the revised Vienna Classification. Levels of agreement in histological grading also increased. Pathologists did not reach consensus even using the revised Vienna Classification in 16.6% of polyp specimens.

CONCLUSIONS

These studies showed that the differences between Western and Japanese pathologists in the diagnostic classification of gastrointestinal epithelial neoplastic lesions can be resolved largely by adopting the newly proposed terminology of the Vienna Classification, which is based on the severity of cytological and architectural changes and on invasion status. Moreover, the authors suggested that the revised Vienna classification not only resulted in the highest agreement scores, but that its categories could also fit best with current clinical considerations.

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3. Stolte M (2003), The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages, *Virchows Arch.*, vol. 442, no. 2, pp. 99-106.

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7.1.2 Evidence tables

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schlemper 2000	Western, Japanese and Vienna classification for gastrointestinal epithelial neoplasia	Study aimed to assess inter-observer agreement among pathologists using Western, Japanese and Vienna classification for gastrointestinal epithelial neoplasia	31 pathologists from 12 countries (20 from Western countries or Korea and 11 from Japan); 20 colorectal lesion	Diagnostic agreement between pathologists assessed by kappa statistic	**Colorectal specimen:** pathologists with a <u>Western viewpoint</u> diagnosis of suspected or definite carcinoma in **5–40%** of the colorectal lesions, pathologists with a <u>Japanese viewpoint</u> diagnosed suspected or definite carcinoma in **45–75%** of the colorectal lesions Percentage of specimens for which there was agreement: **45%** Kappa values: **0.27** (95% CI 0.04-0.49) Percentage of specimens for which there was agreement following <u>Vienna classification</u> (when the original assessments of the specimens were regrouped into the categories of the proposed Vienna classification): **65%** Kappa value: **0.47** (95% CI 0.18-0.76)	

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schlemper 2001	Western, Japanese and Vienna classification for gastrointestinal epithelial neoplasia	Study aimed to assess inter-observer agreement among pathologists using Western, Japanese and Vienna classification for gastrointestinal epithelial neoplasia	31 pathologists from 12 countries (20 from Western countries or Korea and 11 from Japan); 20 colorectal lesion	Diagnostic agreement between pathologists assessed by kappa statistic	**Colorectal specimens**: Japan classification Agreement: 50%; Kappa: 0.30 Western classification Agreement: 45%; Kappa: 0.27 Padova classification Agreement: 65%; Kappa: 0.51 Vienna classification Agreement: 65%; Kappa: 0.47 Vienna revised classification Agreement: 70%; Kappa: 0.54	

Author, publication year	Compared groups	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Suzuki 2006	British patients with adenomatous polyps or cancer matched with 144 Japanese patients with adenoma	Case-control study	Cases: British patients with adenomatous polyps or cancer (n=144) Controls: Japanese patients with adenoma or cancer (n=144)	Interobserver agreement between pathologists assessed by kappa statistic	**Conventional classification** **British pathologists** Kappa: 0.63 for British polyps; Kappa: 0.50 for Japanese polyps; **Japanese pathologists** Kappa: 0.06 for British polyps Kappa: 0.37 for Japanese polyps **Revised Vienna classification** **British pathologists** Kappa: 0.75 for British polyps, (p=0.03)* Kappa: 0.61 for Japanese polyps, (p=0.05)* **Japanese pathologists** Kappa: 0.53 for British polyps, (p<0.001)* Kappa: 0.64 for Japanese polyps, (p<0.001)*	**IV** The discrepancy in histological diagnosis between British and Japanese pathologists is partly resolved by applying the revised Vienna Classification.

*conventional classification (criteria not specified) vs. revised Vienna classification.

Quality assessment: matching only by age, gender; all the colonoscopies were performed by the same colonoscopists, while the histological examinations were performed by two British and two Japanese pathologists.

7.2 Levels of diagnostic reproducibility of the pathological features: dysplasia and villousness in colorectal adenomas

7.2.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 2

What are the levels of diagnostic reproducibility of the pathological features:
- dysplasia
- villousness

in colorectal adenomas?

PICOS

P: Asymptomatic people detected with polyps or symptomatic patients
I: Pathological diagnosis of dysplasia or villousness
C: Not applicable
O: Diagnostic reproducibility/concordance
S: (Systematic reviews of) diagnostic accuracy; cross-sectional studies, population studies; case series

SEARCH METHOD

We contacted experts in the field to retrieve papers relevant to this issue. We also performed a search on MedLine using the following two strategies:
(("Reproducibility of Results"[Mesh]) OR ("Sensitivity and Specificity"[Mesh])) AND ((dysplasia OR villousness) AND (colorectal adenoma)) AND ((Humans[Mesh])). Reproducibility of results (Mesh) AND colorectal neoplasms (Mesh) AND adenoma (Mesh).

RESULTS

We found 80 references, out of which we selected 3 articles relevant to the question.

Two studies assessed the reproducibility of the classification of villousness and dysplasia in adenomas (1,2). Both studies found that the reproducibility was poor both for villousness and dysplasia when 3 or 4 categories were used, but increased when the categories were collapsed into two: tubular vs. any villous component and low vs. high dysplasia. The author of both studies suggested collapsing the categories to increase reproducibility.

One study compared the reproducibility of the classification of adenomas using two different system, the Konishi-Morson system (KMS), a detailed description of the WHO system and the extended Kozuka system (EKS)(3). The study found that both of the systems had a moderate reproducibility but the

reproducibility increased when the KMS systems were collapsed using only two categories: mild/moderate vs. severe. The authors suggested that this simplified KMS should be used

CONCLUSIONS

The reproducibility of villousness and dysplasia was poor or moderate when three or four categories were used, but increased when collapsing the categories into only two: tubular vs. any villous component and low vs. high dysplasia.

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7.2.2 Evidence tables

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Terry 2002	Pathologic classification of villousness and dysplasia of adenomas	Study aimed to assess intra and inter-observer agreement among pathologists for the classification of villousness and dysplasia	104 slides of advanced adenomas and 86 slides of non advanced adenomas from a case control study conducted in three NYC practices form 1986 to 1988. 71 slides from four endoscopy based case control studies conducted in different geographic regions of the USA. Intraobserver agreement assessed comparing the classification of the same pathologist that was made ten years apart. Interobserver agreement assessed comparing the classification made by two pathologists at the same time	Intraobserver and interobserver diagnostic agreement between pathologists assessed by kappa statistic K≤ 50: poor K= 0.51-0.74 moderate K:≥ 75 excellent	**Histological classification (tubular, villous, tubulovillous)** Intraobserver agreement: K 0.28 (CI95%0.17-0.39): fair K: 0.48 (CI95% 0.33-0.62) moderate **Collapsing into 2 categories (tubular, any villous component**: Intra-observer agreement K: 0.36 (CI95% 0.19-0.46) (poor) Inter observer agreement: K: 0.65 (CI95%0.50-0.80) (moderate) **Dysplasia (four categories):** Intra-observer agreement K: 0.20 (CI95% 0.12-0.28) Inter observer agreement: K: 0.42 (CI95% 0.29-0.55); moderate **Dysplasia (two categories: low vs. high)** Intra observer agreement K: 0.32 (CI95% 0.19-0.46) Inter observer agreement: K: 0.69 (CI95% 0.55-0.83) (moderate)	Intra and inter observer agreement was fair to moderate.

Quality assessment: the pathologists were blinded to the original classification and of each other interpretation.

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Yoon 2001	Pathologic classification of villousness and dysplasia of adenomas	Study aimed to assess inter-observer agreement among pathologists for the classification of villousness and dysplasia Interobserver agreement assessed comparing the classification made by two pathologists unaware of the original classification	326 polyps from 148 patients enrolled in the APACC RCT.	interobserver diagnostic agreement between pathologists assessed by kappa statistic K≤ 50: poor K= 0.51-0.74 moderate K:≥ 75 excellent	**Distinction between adenomatous and non adenomatous polyps:** K: 0.67 **Histological classification (2 categories :tubular, any villous component)**: Inter observer agreement: K: 0.46 **Dysplasia (four categories):** Inter observer agreement: K: 0.26 (poor) **Dysplasia (two categories: low vs. high)** Inter observer agreement: K: 0.34 (poor)	Our results indicate the limitation of a colonoscopic surveillance based only on pathology criteria. Our findings also emphasize the importance of improving the reproducibility of histological diagnosis using two level of dysplasia

Quality assessment: the pathologists were blinded to the original classification and of each other interpretation.

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Fenger 1990	Pathologic classification of dysplasia of adenomas using the Konishi-Morson system (KMS), a detailed description of the WHO system and the extended Kozuka system (EKS) KMS: mild, moderate, severe dysplasia EKS: mild, moderate, severe, carcinoma in situ, intramucosal carcinoma	Study aimed to assess intra and inter-observer agreement among pathologists for the classification of dysplasia using two classification system	56 adenomas selected from the files of a department of pathology basing on the original diagnosis and on the requirement that all five grades of EKS system were represented. Intraobserver agreement assessed comparing the classification of the same pathologist made twice. Interobserver agreement assessed comparing the classification made by two pathologists unaware of the original classification	Intra and interobserver diagnostic agreement between pathologists assessed by kappa statistic $K \leq 50$: poor $K= 0.51-0.74$ moderate $K: \geq 75$ excellent	**KMS (three categories):** Intraobserver agreement: K: 0.78, 0.81 Inter observer agreement: K: 0.48 (CI95%0.35-0.61) **KMS (two categories):** mild/moderate vs. severe Inter observer agreement K: 0.80 (excellent) **EKS:** Intraobserver agreement: K: 0.70, 0.68 Inter observer agreement: K: 0.42 (CI95%0.31-0.52)	**V** This study underlines the discrepancies between the two grading system, none of which has impressive overall interobserver reproducibility. By modifying the KMS into two categories, however, an excellent overall interobserver reproducibility was found. We therefore propose that this simplified KMS is used

Quality assessment: not specified if the pathologists were blinded to the original classification and of each other interpretation. Not specified the time elapsed between the two classification for intra-observer agreement.

7.3 Frequency of high grade dysplasia (HGD), villousness, size >10 mm in people detected with polyps in flexible sigmoidoscopy/ FOBT/colonoscopy studies

7.3.1 Summary document

Silvia Minozzi and Rita Banzi

CLINICAL QUESTION 3

What is the actual proportion of high grade dysplasia (HGD), villousness, size >10 mm in flexible sigmoidoscopy/ FOBT/colonscopy studies?

PICOS

P: Asymptomatic people detected with polyps in flexible sigmoidoscopy/ FOBT/colonoscopy studies
I: FOBT; flexible sigmoidoscopy, colonoscopy
C: Not applicable
O: Frequency of pathological diagnosis of HGD, villousness or size >10 mm
S: (Systematic reviews of) trials; cross-sectional studies, population studies; case series

SEARCH METHOD

We contacted experts in the field to retrieve papers relevant to this issue. We analysed studies already used for Chapter 3.

RESULTS

We found 11 studies relevant to the questions of this chapter. Four were cross-sectional surveys reporting baseline results of screening with sigmoidoscopy (1,2,4,5), four with colonoscopy (6,7,9,10), one was a randomised trial comparing FOBT and sigmoidoscopy (8) and one a randomised trial comparing FOBT, colonoscopy and sigmoidoscopy (3). One specific RCT on FOBT screening was also included as it reported data on this topic (11). All studies screened people at average risk of colorectal cancer.

Sigmoidoscopy studies
All studies screened people at average risk of colorectal cancer aged 55-64 years; one (1) included people until 74 years.

2 studies reported the results separately for the frequency of HDG, villousness and adenomas >1 cm (2, 5)

4 studies reported only the frequency of high risk adenoma defined as an adenoma measuring ≥ 10 mm, with villous component and/or showing severe dysplasia (1,2,3,8).

The results are shown in table 1

Colonoscopy studies

Four studies screened people at average risk of colorectal cancer; one included also people with family risk but reported results separately for subgroup; thus we report here only the results of people without family history of CRC (9). Age of participants varied among studies.

Four studies reported the results separately for the frequency of HDG, villousness and adenomas >1 cm (6,7,9,10).

One study reported only the frequency of high risk adenoma defined as an adenoma measuring ≥ 10 mm, with villous component and/or showing severe dysplasia (3)

The results are shown in table 2

FOBT studies

Data are summarised in table 3. The SCORE studies, which compared FOBT to endoscopic screening programmes reported similar results both in terms of rate of positive FOBT and incidence of advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia) (8,3). Lower frequencies were reported in the Nottingham trial (11).

CONCLUSIONS

The frequency of High degree dysplasia ranged from 0.6% to 1.1% of people screened.

The frequency of villousness ranged from 1.6% to 3% of people screened.

The frequency of adenomas greater than 1 cm ranged from 3.1% to 8.5%.

The frequency of high risk adenomas ranged from 1.2% to 6.3% of people screened.

The variability observed in the frequency of adenomas with high degree dysplasia, villousness and size >1 cm could be attributed both to differences in the populations screened and to the non optimal reliability of pathological diagnosis (LEVEL OF EVIDENCE V).

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7.3.2 Evidence tables

Table 1. Studies on sigmoidoscopy

	NORCCAP 2003 (5)	PLCO 2005 (1)	SCORE (4)	UK FSST 2002 (2)	SCORE 3 (3)	SCORE 2 (8)
People screened	12960	64658	9911	40674	1922	4466
Age of participants	55-64	55-74	55-64	55-64	55-64	55-64
People with positive results (polyp or mass)		15150 (23.4%)	17.6%	10258 (27%)		
People with adenomas	2208 (17% of people screened)		1070 (10.8% of people screened)	4931 (12% of people screened)	214 (11.2% of people screened)	535 (12% of people screened)
High degree dysplasia /severe dysplasia	149 1.1% of people screened 6.7% of people with adenomas			301 0.7% of people screened 6.1% of people with adenomas		
Villousness	213 1.6% of people screened 9.6% of people with adenomas			964 2.4% of people screened 19.5% of people with adenomas		
Size >1 cm	428 3.3% of people screened 19.4% of people with adenomas			1293 3.2% of people screened 12.6% of people with adenomas		
Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia)		19.1% of people with positive results	120 1.2% of people screened 11.2% of people with adenoma		88 4.6% of people screened 41% of people with adenomas	229 5.1% of people screened 42.8% of people with adenoma

Table 2. Studies in colonoscopy

	Lieberman 2000 (7)	Schoenfeld 2005 (6)	Regula 2006 (9)	Sung 2003 (10)	SCORE 3 (3)
People screened	3121	1463	37313 (subgroup 50-66 years at average risk)	476	1596
Age of participants	50-74; only men	50-79; only women	50-66	>50 years	55-64
People with positive results (polyp or mass)	1680 (53.8%)		25%	152 (31.9%)	
People with adenomas	1141	299 20.4% of people screened	5046 (13.5% of people screened)	102	187 (11.7% of people screened)
High degree dysplasia /severe dysplasia	51 0.7% of people screened 4.4% of people with adenoma	9 0.6% of people screened 3% of people with adenoma	326 0.9% of people screened 6.4% of people with adenomas		
Villousness	94 3% of people screened 8.2% of people with adenoma	26 1.8% of people screened 8.7% of people with adenoma	901 2.4% of people screened 17.8% of people with adenoma	9 1.9 % of people screened 8.8 % of people with adenomas	
Size >1 cm	264 8.5% of people screened 23% of people with adenoma	46 tubular adenomas 3.1% of people screened 15.4 % of people with adenoma	1156 3% of people screened 22.9% of people with adenoma	19 4% of people screened 18.6% of people with adenomas	
Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia)		72 4.9% of people screened 24% of people with adenoma			100 6.3% of people screened 53,5% of people with adenoma

Table 3. Studies in FOBT

	SCORE 2 (8)	SCORE 3 (3)	NOTTINGHAM STUDY (11)
People screened	2858	1965	75253
Age of participants	55-64 years	55-64 years	45–74 years
People with positive FOBT	122 (4.3% of the screened population)	92 (4.7% of the screened population)	837 (2.1% of the screened population)
People underwent endoscopy	107 (87.7% of the FOBT positive population)	81 (88.0% of the FOBT positive population)	Not reported
People with adenomas (positive colonoscopy)	41 (38.3% of the endoscopy screened population)	37 (45.7% of the endoscopy screened population)	710 (0.94% of the screened population)
High degree dysplasia /severe dysplasia	Not reported	Not reported	97 (0.13% of the screened population; 13.6% of adenomas)
Villousness	Not reported	Not reported	Not reported
Size >1 cm	Not reported	Not reported	582 (0.77% of the screened population; 82% of adenomas)
Advanced adenomas (villous or tubulovillous, size ≥ 1 cm or severe or high grade dysplasia)	39 (36.4% of the endoscopy screened population; 95% of people with adenomas)	21 (25.9% of the endoscopy screened population; 56.7% of people with adenomas)	-

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Weissfeld 2005 PLCO	Flexible sigmoidoscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of RCT PLCO	Random sample of general population aged 55-74 years n. 77465 USA	Positive results: polyp or mass) Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia)	positive rates: 23.4% Advanced adenomas: 19.1% of people with positive results	V Authors underline that the compliance was high

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
UK FS screening trial Investigators 2002	Flexible sigmoidoscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of multicentre RCT in UK	Random sample of general population aged 55-64 years n. 57254 UK	Positive results: polyp or mass People with adenomas High degree dysplasia /severe dysplasia Villousness Size >1 cm	Positive results: 27% People with adenomas: 4931 (12% of people screened) High degree dysplasia /severe dysplasia: 301 0.7% of people screened 6.1% of people with adenomas Villousness: 964 2.4% of people screened 19.5% of people with adenomas Size >1 cm: 1293 3.2% of people screened 12.6% of people with polyps	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2007 (SCORE 3)	1.biennial immunologic FOBT (FIT) 2. once only colonoscopy 3.once only sigmoidoscopy	Multicentre RCT	Random sample of general population aged 55-64 years n. 18477 Italy	Positive results: polyp or mass Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia)	Positive rates: Fit: 4.7% FS: 18.9% Colonoscopy :31.1% Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia) Fit: 21 1.1% of people screened FS: 88 4.6% of people screened Colonoscopy :100 6.3% of people screened	II

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is feasible for the kind of intervention compared.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2002 (SCORE)	Once only sigmoidoscopy	Cross-sectional survey: reported the findings of baseline screening FS arm of RCT SCORE	Random sample of general population aged 55-64 years n. 17148 Italy	Positive results: polyp or mass People with adenomas Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia)	Positive results:17.6% People with adenomas: 1070 (10.8% of people screened) Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia): 120 1.2% of people screened 11.2% of people with adenoma	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Gondal 2003 NORCCAP study	1.one only FS 2. once only FS + FOBT immunochemical	RCT	Random sample of general population aged 55-64 years n= 20,003 Norway	Positive results: polyp or mass People with adenomas High degree dysplasia /severe dysplasia Villousness Size >1 cm	<u>Positive results.</u> All FS : 20.4% People with adenomas: 2208 (17% of people screened) High degree dysplasia /severe dysplasia: 149 1.1% of people screened 6.7% of people with adenomas Villousness: 213 1.6% of people screened 9.6% of people with adenomas Size >1 cm: 428 3.3% of people screened 19.4% of people with adenomas	**II**

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schoenfeld 2005	colonoscopy	Cross-sectional survey	Consecutive average risk asymptomatic 50-79 years old women referred for CRC screening at four military centres. n= 1,539 USA	People with adenomas High degree dysplasia /severe dysplasia Villousness Tubular adenoma of Size >1 cm Advanced adenomas	People with adenomas: 299 High degree dysplasia /severe dysplasia: 9 0.6% of people screened 3% of people with adenoma Villousness: 26 1.8% of people screened 8.7% of people with adenoma Tubular adenoma of Size >1 cm: 46 3.1% of people screened 15.4 % of people with adenoma Advanced adenomas: 72 4.9% of people screened 24% of people with adenoma	**V**

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Lieberman 2000	Colonoscopy	Cross-sectional survey:	Randomly selected average risk asymptomatic 50-75 years old men referred for CRC screening at 13 VA medical centres. n= 3,196 USA	Positive results: polyp or mass People with adenomas High degree dysplasia /severe dysplasia Villousness Size >1 cm	Positive results: 1680 (53.8%) People with adenomas: 1141 High degree dysplasia /severe dysplasia: 51 0.7% of people screened 4.4% of people with adenoma Villousness: 94 3% of people screened 8.2% of people with adenoma Size >1 cm: 264 8.5% of people screened 23% of people with adenoma	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Segnan 2005 (SCORE 2)	1.biennial immunologic FOBT delivered by mail 2. biennial immunologic FOBT delivered by GP 3 once only sigmoidoscopy 4. FS followed by biennial FOBT 5 patient choice between once only FS and FOBT	Multicentre RCT	Random sample of general population aged 55-64 years N= 26,682 Italy	Positive results: polyp or mass Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia	Ppositive results: FOBT (1+2+5): 4.3% FS (3+4+5): 18.6% Advanced adenomas (villous or tubulovillous , size ≥ 1 cm or severe or high grade dysplasia FS: 229 5.1% of people screened 42.8% of people with adenoma FOBT: 39 2.3% of people screened 95% of people with adenoma (people with adenoma: 41)	II

Quality assessment: avoidance of selection bias: adequate allocation concealment; performance bias: not applicable; protection against contamination: spouses allocated to the same arm; attrition bias: not applicable: participation is the primary outcome and the other outcomes are related to test performance; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives and because it is not feasible for the kind of intervention compared.

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Regula 2006	colonoscopy	Cross-sectional survey:	Randomly selected average risk asymptomatic 40-66 years old men referred for CRC screening. People 40-49 years included if they had family history of cancer of any type n= 50,148 Poland	Positive results: polyp or mass High degree dysplasia /severe dysplasia Villousness Size >1 cm	Results of the 37.313 50-66 years old at average risk positive results: 25% High degree dysplasia /severe dysplasia: 326 0.9% of people screened 6.4% of people with adenomas Villousness: 901 2.4% of people screened 17.8% of people with adenoma Size >1 cm : 1156 3% of people screened 22.9% of people with adenoma	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Sung 2003	FOBT, colonoscopy	Cross-sectional survey: subjects underwent FOBT (guaiac hemoccult II) without dietary restriction and colonoscopy	Asymptomatic subjects older than 50 years recruited on a voluntary basis China n= 505	Positive results: polyp or mass Villousness Size >1 cm	Positive results: 31.9% Villousness: 9 1.9% of people screened 8.8% of people with adenoma Size >1 cm : 19 4% of people screened 18.6% of people with adenoma	V

Author, publication year	Experimental and control Intervention	Study design	Participants	Outcome	Follow up	Results	Level of evidence Conclusions
Hardcastle 1996 Nottingham	Biennial Hemoccult screening groups Control group: no screening	RCT	45–74 years 152,850 (75,253 FOB screening; 74,998 no screening)	CRC mortality reduction, CRC incidence, Number of CRC deaths, Death from all causes	7.8 years follow-up	Positive FOBT: 837 (2.1% of the screened population) Screen-detected adenomas: 710 Adenomas ≥ 10 mm: 582 (82%) (128 adenomas were less than 10 mm (18%) 375 were 10–19 mm (52.8%) 207 were 20 mm or more (29%)	II

Quality assessment: adequate randomisation procedure, adequate allocation concealment. Individual random allocation of subjects who lived in the Nottingham area (stratified by age, sex and place of residence). Blinding of the participants not applicable. Analysis by intention to screen. High rate of subjects completed at least one offered screening (60%). Blinded, standardised assessment of CRC mortality.

7.4 Evaluation of differences in the detection rate of non polypoid colorectal neoplasms among different types of screening programmes

7.4.1 Summary document

Rita Banzi

CLINICAL QUESTION 4

Are there significant differences in the detection rates of non polypoid colorectal neoplasms (flat adenomas, depressed adenomas, lateral spreading tumours) among the different types of screening programmes (FOBT vs. FS vs. colonoscopy)?

PICOS

P: Asymptomatic people detected with polyps in flexible sigmoidoscopy/ FOBT/colonoscopy studies
I: FOBT
C: FS, colonoscopy
O:Detection rate of Nonpolypoid Colorectal Neoplasms (flat adenoma, depressed adenoma, Paris Classification)
S: (Systematic reviews of) trials flexible sigmoidoscopy/ FOBT/colonoscopy studies; cross-sectional studies, population studies; case series

SEARCH METHOD

We searched <u>MedLine</u> databases from 1998 using the following search strategy:
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* OR "Adenomatous Polyps"[Mesh]) AND
((sessile OR sessile) OR non polypoid neoplasm* OR "flat adenoma" OR depressed adenoma OR lateral spreading tumour* OR lateral spreading tumour* OR lateral spreading cancer* OR lateral spreading neoplasm* OR Paris classification) AND (("Sensitivity and Specificity"[Mesh] OR specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*) AND ("Colonography, Computed Tomographic"[Mesh] OR Flexible sigmoidoscopy OR "Sigmoidoscopy"[Mesh] OR "Guaiac"[Mesh] OR "Occult Blood"[Mesh] OR faecal occult blood test OR immunochemical test*)

We also searched the <u>Cochrane Library</u> and retrieved additional papers from the analysis of the quoted bibliography.

Finally we looked at the results of studies already considered for Chapter 3 and question 3 of Chapter 8, which are studies which present the baseline results of community based screening programmes using FOBT, sigmoidoscopy and colonoscopy to see if also the detection rate of non polypoid neoplasms (flat /depressed adenomas) were reported.

RESULTS

We were unable to retrieve studies which directly compared the detection rate of different type of CRC screening programmes (FOBT, flexible sigmoidoscopy, and colonoscopy) with regard to non-polypoid colorectal neoplasms. We found no studies regarding FOBT and flexisigmoidoscopy detection rate of nonpolypoid colorectal neoplasms.

We found four RCTs (1-4) and a cross-sectional study (5) which have compared the diagnostic yield of conventional colonoscopy versus chromoscopic colonoscopy with regard to non polypoid lesions.

The first RCT conducted in the UK randomised 260 consecutive patients referred to one hospital for colonoscopy to standard colonoscopy (with saline spray) or pan-colonic chromoendoscopy (1). A significantly higher number of diminutive (<4 mm) and flat adenomas were detected in the pan-chromoscopy group compared with controls (p<0.01).

Another RCT compared high resolution colonoscopy (HRC) coupled with pancolonic indigo carmine chromoscopy (SC) in a French population at increased risk of colonic neoplasia (2). A pre-planned interim analysis was performed after the inclusion of 200 patients (100 in each group): 203 patients (age: 58±10 years) with a history of either familial or personal colonic neoplasia or with alarm symptoms were enrolled. A significant increase in the number of purely flat adenomas, polyps, and hyperplastic polyps was detected in the colon with HRC. The number of purely flat adenomas was significantly higher in the HRC group than in the SC group (0.22±0.68 vs. 0.07±0.29, respectively; p=0.04). HRC revealed more flat adenomas >5 mm in diameter than SC (0.12±0.05 vs. 0.03±0.17; p=0.09), whereas there was no significant difference between the numbers of flat adenomas ≥5 mm detected by HRC and SC (0.10±0.39 vs. 0.04±0.20, respectively; p=0.17).

Rex et al. reported in an RCT conducted in the USA their experience of pancolorectal narrow-band imaging (NRI) versus high-definition white light (HDWL) for the detection of colorectal adenomas in the intact colon (3). Narrow-band imaging (NBI) enables, via the application of narrow bandwidth filters to standard white-light endoscopy, clear definition of the contrast between the epithelial surface and the adjacent vascular net. The RCT results (434 patients aged 50 years or older) showed no difference in the percentage of patients with adenomas (any size) for the entire cohort or in the subgroup of 257 patients where the indication was screening. No significant difference in any type of adenoma and flat adenoma was found between the two groups (overall mean rate of adenoma detection (±SD) white light: 1.8 (±2.2) NBI: 1.9 (±2.5), p=0.68 and rate of flat adenomas white light: 1.0 (±1.4) NBI: 1.0 (±1.5) p=0.98).

Similar data were reported in another RCT which compared NBI versus wide-angle high-resolution WLC. (4) From a total recruitment cohort of 401 patients, when the 2 techniques were compared in consecutive subgroups of 100 study patients, adenoma rates in the NBI group remained "stable," whereas the rates increased sequentially in the WLC control group. Hence, the adenoma detection rates differed significantly in the first 100 patients (NBI 26.5%, control group 7.8%; p=0.02), but not in the last 100 cases (26.5% versus 25.5%; p=0.91). Sub analysis did not show that small adenomas (<10 mm) or sessile/flat adenomas were more frequently detected with increasing NBI experience in the non- NBI group (p=0.156 and p=0.536, respectively).

An Italian cross-sectional study compared the diagnostic performance of chromoendoscopy performed only in those patients with suspicious mucosal areas at conventional colonoscopy (5). 305 out of 2,005 (15%) patients underwent chromoendoscopy which detected 244 additional neoplastic lesions in 212 patients (11%), all with non polypoid characteristics. Thus, while all polypoid lesions and the advanced cancers were identified during conventional colonoscopy, 35% of non-advanced neoplasms were detected only after CE, and all lesions were non-polypoid.

CONCLUSIONS

A prevalence of 9-10% of non polypoid colorectal neoplasm (flat and depressed) was recently reported by Western pathologists in a large cross-sectional study (6). We were unable to retrieve studies which specifically address the topic of the differences in the DRs of non polypoid colorectal neoplasms among the different types of screening programmes (FOBT vs. FS vs. colonoscopy).

We only found evidence that chromoscopy enhances the detection of premalignant polyps in the colon and rectum, including non polypoid lesion when compared with conventional colonoscopy (LEVEL OF EVIDENCE II).

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7.4.2 Evidence tables

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Hurlstone 2004	RCT	Standard colonoscopy (SC) versus pan-colonic chromoscopy	260 consecutive patients attending for routine colonoscopy (132 controls and 128 pan-colonic chromoscopy) UK		Rate of adenoma detection	***Number of flat lesion detected according to histology*** Control Group Hyperplastic: 31 LGD: 18; HGD: 4 Pan-chromoscopy group Hyperplastic: 28 LGD: 37; HGD: 17 ***Total number of lesions*** 289 lesions in 138 patients. Control group: 103 (36%) Pan-chromoscopy group: 185 (64%) ***Median number of lesions*** 0 (range 0–24) ***Number of hyperplastic lesions*** 117 (41%) Control group: 45 (38%) Pan-chromoscopy group: 72 (62%) (p<0.001) ***Number of flat hyperplastic lesions*** 59 (51%) ***Number of protuberant hyperplastic lesions*** 58 (49%) ***Number of neoplastic lesions*** 170 (59%); 168 (98%) were adenomas Control group: 57 (33%) Pan-chromoscopy group: 112 (66%) p<0.05 ***Number of flat adenoma*** 76 (45%) ***Number of protuberant adenoma*** 92 (55%)	II Pan-chromoscopy diagnosed more diminutive and flat lesions in the right colon compared with controls (p<0.05). Hyperplastic lesions were more commonly detected in the pan-chromoscopy group compared with controls (p<0.001). A significantly higher number of diminutive (<4 mm) and flat adenomas were detected in the pan-chromoscopy group compared with controls (p<0.01).

Quality assessment: Allocation sealed envelopes drawn at time of caecal intubation (information not reported in the original publication but retrieved from the Cochrane Review Brown SR, Baraza W, Hurlstone P. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD006439. DOI:10.1002/14651858.CD006439. pub2); Blinding not applicable; Withdrawals: None; Intention-to-treat analysis: Randomisation on caecal intubation. No withdrawals.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Le Rhun 2006	RCT	Standard colonoscopy (SC) versus high-resolution colonoscopy with chromoscopy (HRC)	203 patients with a history of either familial or personal colonic neoplasia or with alarm symptoms aged 58±10 years; France	-	Rate of adenoma detection	***Number of polyps per patient*** SC: 1.1±1.8 HRC: 1.7±2.0 p=0.01 ***Number of adenomas per patient*** SC: 0.5±0.9 HRC: 0.6±1.0 p=NS ***Number of purely flat adenomas per patient*** SC:0.07±0.29 HRC:0.22±0.68 p=0.04 ***Number of hyperplastic polyps per patient*** SC:0.5±1.4 HRC:1.1±1.6 p=0.01	**II** A significant increase in the number of purely flat adenomas, polyps, and hyperplastic polyps was detected in the colon with HRC. The number of purely flat adenomas was significantly higher in the HRC group than in the SC group (0.22±0.68 vs. 0.07±0.29, respectively; p=0.04). HRC revealed more flat adenomas <5 mm in diameter than SC (0.12±0.05 vs. 0.03±0.17; p=0.09), whereas there was no significant difference between the numbers of flat adenomas ≥5 mm detected by HRC and SC (0.10±0.39 vs. 0.04±0.20, respectively; p=0.17). There were 2 adenomas with high-grade dysplasia in the SC group versus 0 in the HRC group (not significant) Chromoscopy is not expected to improve the detection of protrusive or large lesions (which can be easily identified without indigo carmine) but rather the diagnosis of small tiny lesions.

Quality assessment: central randomisation; sequence generated by using computer-generated random numbers (blocking with randomly varying groups of 6–8; centre stratification); sealed envelopes containing the intervention assigned; interim analysis at 100 patients (50% of the sample size).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Rex 2007	RCT	Colonoscopy using white light versus narrow band imaging (NBI) which enables, via the application of narrow bandwidth filters to standard white light endoscopy, clear definition of the contrast between the epithelial surface and the adjacent vascular net.	434 patients aged 50 years or older with intact colons undergoing colonoscopy for colorectal cancer screening, postpolypectomy surveillance, or other indications for which the primary goal of the examination was detection of neoplasia USA	-	Number of adenomas	***Total adenomas detected*** White light: 395 NBI: 403 p=0.68 ***Total adenomas 0–5 mm*** White light: 340 NBI: 346 p=0.93 ***Total adenomas 6–9 mm*** White light: 31 NBI: 38 p=0.85 ***Total adenomas ≥1 mm*** White light: 14 NBI: 16 p=0.67 ***Overall mean rate of adenoma detection (±SD)*** white light:1.8 (±2.2) NBI:1.9 (±2.5) p=0.68 ***Rate of flat adenomas*** White light:1.0 (±1.4) NBI:1.0 (±1.5) p=0.98	**II** NBI in this study did not result in improvements in detection of adenomas when it was tested by a single examiner with a known high detection rate for adenomas with white light colonoscopy. Whether NBI could improve detection of adenomas by colonoscopists with low adenoma detection rates using white light and thereby reduce the variation in adenoma detection between examiners deserves additional evaluation.

Quality assessment: Consecutive outpatients presenting to Indiana University Hospital. Randomisation was performed using a computer-generated randomisation scheme using block sizes of 10. Randomisation to withdrawal in white light versus NBI was performed after the tip of the colonoscope reached the cecum. 19 patients were enrolled in the study but were excluded before randomisation because of poor or inadequate bowel preparation. Allocation in a sealed envelope, blinding not applicable, control of contamination (100% of the mucosal inspection for polyps during withdrawal in every patient was performed with the light designated by the randomisation); attrition bias: no information on subjects screened but not randomised-other lost at follow up non applicable; all the colonoscopy were performed by the same investigator.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Adler 2008	RCT	Wide-angle colonoscopy using Narrow Band Imaging versus wide-angle versus high-resolution White Light Colonoscopy	410 patients (mean age 59.4 years, 52.6% men)	-	Primary: number of adenoma. Secondary: • total number of polyps in both groups • total number of flat/sessile adenomas in both groups • total number of adenomas less than 1 cm in both groups • total number of hyperplastic polyps and hyperplastic polyps less than 1 cm in both groups • Right-sided versus left-sided location in both groups.	*Overall polyp detection rate (polyps of all histology)* 33.6% (n=133), adenomas 19.9% (n=79) hyperplastic polyps 19.7% (n=78) *Patients with polyps (n, %)* NBI group: 82 (41.4) Control group: 51 (25.8) OR=2.0 (1.3–3.1) p=0.001 *Patients with adenomas (n, %)* NBI group: 45 (22.7) Control group: 33 (16.7) OR=1.5 (0.9–2.4) p=0.129 *All polyps (n)* NBI group: 171 Control group: 83, p=0.001 *Polyps <10 mm* NBI group: 152 Control group: 75, p=0.361 *All adenomas (n)* NBI group: 65 Control group: 51, p=0.158 *Adenomas <10 mm* NBI group: 41 Control group: 37, p=0.156 *Flat/sessile* NBI group: 49 Control group: 28, p=0.536	**II** Although 36% more adenomas were found by NBI, the difference was not statistically significant for the total study group. Analysed on a number-needed-to-diagnose basis, 17 colonoscopies would be required to detect one additional adenoma patient by means of NBI. Adenoma rates in the NBI group remained fairly stable, whereas these rates steadily increased in the control group (8%, 15%, 17%, and 26.5%, respectively). We found that the adenoma detection rates differed significantly in the first 100 patients (NBI 26.5%, control group 7.8%; p=0.02), but not in the last 100 cases (26.5% versus 25.5%; p=0.91). We hypothesised that improved recognition of lesions on NBI may also subsequently have improved the examiners' ability to perceive such lesions on conventional high-resolution colonoscopy, although the study was not set out and powered to test a possible learning effect. Sub analysis did not show that small adenomas (<10 mm) or sessile/flat adenomas were more frequently detected with increasing NBI experience in the non-NBI group, probably because of limited numbers in the subgroups.

Quality assessment: Unit of allocation and analysis were patients. Information on the generation of the random sequence and concealment of allocation were not provided (Randomisation lists were used for group allocation). Blinding not applicable. Blinding of the outcome assessor not applicable. Withdrawal rates and reasons reported (five patients were excluded secondarily during the study audit as a result of violation of the protocol).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Trecca 2006	Cross-sectional study	Conventional colonoscopy and chromoendoscopy (CE) performed only in those patients with suspicious mucosal areas All examinations were carried out by the same operator	2,712 colonoscopic examinations: patients with a previous diagnosis of colorectal polyps (n=242), inflammatory bowel diseases (n=101), history of colorectal surgery (n=41), high coagulative risk (n=14), poor bowel preparation (n=269) and missing final histological results (n=40) were excluded. Final study population: 2,005 patients with a median age 52 years (range, 18–89) female/male ratio 1.6:1 305 (15%) underwent conventional colonoscopy. Italy	-	Comparison between results of conventional endoscopy and CE. Diagnostic accuracy of conventional colonoscopy vs. CE was then calculated considering histological examination the end-point of the study (adenoma and CRC)	***Number of patients underwent CE because of suspicious areas found at colonoscopy*** 305/2005 (15%) ***Number of neoplastic lesions found with conventional colonoscopy:*** 508 in 381 patients (381/2005, 19%) ***Additional neoplastic lesions found with selective CE*** 244 in 212 patients (212/2005, 11%). ***Positive CE in whom the examination was performed*** 212/305 (70%) ***Number of Advanced cancers detected (overall)*** 56/2005 (2.8%) ***Number of Non-advanced neoplasms detected (overall)*** 696/2005 (34.7%) Polypoid: 448 (64%) (all identified during conventional colonoscopy) Non-polypoid: 248 (36%); of these 236 were flat and 12 depressed Found only after CE: 244/696 (35%, all non-polypoid) Non-polypoid lesions detected using conventional colonoscopy: 4/696 (0.6%, all greater than 10 mm in diameter) ***Number of HGD among the non-polypoid lesion*** 33/248 ***Number of early adenocarcinoma among the non-polypoid lesion*** 6/248 ***Prevalence of advanced histology (HGD + early adenocarcinoma)*** 15% Analysing the non-polypoid lesions by subgroup, the depressed lesions were more likely to have advanced histology than the flat ones. (58% vs. 13%, $p<0.001$; Fisher's exact test)	**V** All polypoid lesions and the advanced cancers were identified during conventional colonoscopy. 35% of non-advanced neoplasms were detected only after CE and all lesions were non-polypoid. A selective chromoendoscopy in the presence of endoscopic clues of non-polypoid lesions should be recommended.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Soetikno 2008	Cross-sectional study	Colonoscopy	1819 subjects underwent colonoscopy: 616 subjects in the screening population (asymptomatic patients who underwent average risk-screening colonoscopy for CRC); 654 subjects in the surveillance population (who had surveillance colonoscopy because of personal or family history of CRC or cancer); 549 subjects in the symptomatic population (who had anemia, rectal bleeding, constipation, diarrhea, positive results from a faecal occult blood test, weight loss, abdominal pain, and inflammatory bowel disease that may be attributed to having colorectal neoplasms. Mean age 64 (SD 11) California	3 Years or Less	Prevalence of nonpolypoid (NP-CRN) colorectal neoplasm and CRC Advanced Neoplasia at Follow-up Colonoscopy	***Subjects with at least one superficial colorectal neoplasm*** 764 (42%) ***Prevalence of NP-CRN*** Overall: 170 (9.35%; 95% CI 8.05%-10.78%) Flat: 156 (8.58%; 95% CI 7.33%-9.96%) Depressed: 18 (0.99%; 95% CI, 0.59%-1.56%) Only neoplasms of nonpolypoid shape: 89 (5%; 95% CI 3.94%-5.99%) Both nonpolypoid and polypoid neoplasm: 81 (4.4%; 95% CI 3.55%-5.50%) Only polypoid neoplasms: 594 (33%; 95% CI 30.5%-34.9%) ***Prevalence in the screening population*** Prevalence of NP-CRNs: 36 (5.84%; 95% CI, 4.13%-8.00%); OR=2.80 (95% CI 1.31-5.98); ***Prevalence in the surveillance population*** Prevalence of NP-CRNs: 101 (15.44%; 95% CI 12.76%-18.44%); OR=3.30 (95% CI 1.86-5.86); ***Prevalence in the symptomatic population*** Prevalence of NP-CRNs: 33 (6.01%; 95% CI, 4.17%-8.34%) OR=3.39 (95% CI 1.46-7.88). ***Patients with follow-up colonoscopy*** 393/580 (68%); advanced CRC: 13	**V** This study provide supporting evidence that NP-CRNs are a relatively common finding among white patients in a single Veterans Affairs population, with a prevalence of 9.3%. The prevalence in patients undergoing colonoscopy for screening, surveillance, and symptoms are 5.8%, 15.4%, and 6.0%, respectively

Quality assessment: cohort representative of men; adequate assessment of outcome; preliminary data on the incidence of advanced neoplasia at the follow up colonoscopy.

7.5 Importance of site of primary tumour and pathological features to predict lymph node metastasis or local recurrence and the levels of reliability and diagnostic reproducibility of these pathological features

7.5.1 Summary document

Rita Banzi

CLINICAL QUESTIONS 5 AND 6

In T1 adenocarcinoma what is the importance of site of the primary tumour and which of the following pathologic features best predict lymph node metastasis or local recurrence for management decisions (surgery vs. surveillance) of cancerized adenomas?

Which are the levels of reliability and diagnostic reproducibility of these pathologic features?

- incomplete excision (if yes 0mm or 1mm or 2mm)
- lymphatic invasion
- vascular invasion
- poor differentiation/high grade
- budding of glands on invasive border (tumour budding)

PICOS

P: People diagnosed with T1 adenocarcinomas (pT1 colorectal cancer, adenoma containing invasive carcinoma, submucosal carcinoma, malignant polyp)
I: Site of primary tumour Pathological featuring of cancerized adenomas (lymphatic invasion, vascular invasion, poor differentiation/high grade, budding of glands on invasive border (tumour budding)
C: Not applicable
O: Frequency of lymph node metastases or local recurrence of adenoma or adenocarcinoma at site of lesion; Patient's management decision (surgery vs. surveillance); Reproducibility of the histological features
S: (Systematic reviews of) trials flexisigmoidoscopy /colonoscopy studies; cross-sectional studies, population studies; case series

SEARCH METHOD

We searched <u>MedLine</u> and <u>Embase</u> databases. Due to the PICOs complexity we used separate strategies to address the question 1) "which tumour primary site and pathologic features best predict

lymph node metastasis or local recurrence" and 2) "which are the levels of reliability and diagnostic reproducibility of pathologic feature, such as incomplete excision, lymphatic invasion, vascular invasion, poor differentiation/high grade, budding of glands on invasive border" respectively.

For the first question, which is related to prognosis outcomes, we used the following search strategies:

"tumour primary site"
"Colonic Polyps"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* AND site* cancer* OR site* neoplasm* OR site* tumour* AND "Neoplasm Staging"[Mesh] OR staging AND metastasis OR recurrence* OR "Neoplasm Recurrence, Local"[Mesh] OR "Lymphatic Metastasis"[Mesh]

"pathologic features"
("Colonic Polyps"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (excision OR "lymphatic invasion" OR "vascular invasion" OR budding OR "poor differentiation" OR "high grade" OR "Neoplasm Invasiveness"[Mesh]) AND ("Neoplasm Staging"[Mesh] OR staging AND metastasis OR recurrence* OR "Neoplasm Recurrence, Local"[Mesh] OR "Lymphatic Metastasis"[Mesh]) AND T1

For the second question, which is related to diagnostic accuracy outcomes, we used the following search strategy:

("Colonic Neoplasms"[Mesh]OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* AND T1 OR T2 OR T3 OR T4 OR pT1 OR pT2 OR pT3 OR pT4) AND (excision OR "lymphatic invasion" OR "vascular invasion" OR budding OR "vein invasion" OR differentiation OR grade OR "Neoplasm Invasiveness"[MeSH] AND Reproducibility of results[MH] OR specimen handling[MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation[MH] OR quality assurance OR quality control OR specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*)

We also searched the Cochrane Library and we retrieved additional studies from the analysis of literature quoted in the considered papers.

RESULTS

Eleven studies were considered relevant for part 1 of this issue: one systematic review (1), one prospective cohort study of patients included in a RCT (2), one prospective cohort study (5), four cross-sectional studies (3,4,6,8), three retrospective cohort studies (7, 9, 10) and one case-control study. (11) Results are summarised in Table 1.

The pooled analysis performed by Hassan et al. on 31 studies including 1,900 patients allowed the evaluation of the specific predictive value of the three selected risk factors simultaneously: positive resection margin, poor differentiation, and vascular invasion (1). The analysed outcome were 1) residual disease; 2) recurrent disease; 3) lymph node metastasis; 4) hematogenous metastasis; 5) mortality. A positive resection margin was found to be largely predictive of local disease (OR 15; 95% CI 5.3–42.7); the presence of poorly differentiated carcinoma is mainly associated with a higher cancer-related mortality (OR 9.2; 95% CI 4.7–18.3); and vascular invasion with a higher risk of lymph node metastasis (OR 7; 95% CI 2.6–19.2).

Lymph node metastasis
The association between the proposed histologic risk factors and the occurrence of lymph node metastasis was also reported in six studies (3, 4, 6-8, 10). A cross-sectional study conducted in the

United States on 159 patients (48 T1, 111 T2) with localized rectal tumours technically amenable to local excision showed that tumours with blood vessel invasion had a significantly (p=0.04) increased (2.5-fold higher) risk of lymph node metastasis compared with tumours without blood vessel invasion; while tumours with lymphatic vessel invasion or poor differentiation had only a higher likelihood (p=not significant) of regional lymph node metastasis. (3) In this study, the risk stratification analysis showed that the presence of blood vessel invasion, lymphatic vessel invasion, or poor differentiation in the primary tumour identifies a population with a significantly higher risk of lymph node metastasis. On the other hand, a similar Japanese study (101 pT1 or pT2 well-differentiated colorectal adenocarcinomas) reported a higher prevalence of lymph node metastasis in tumours with lymphatic invasion (p<0.0001), venous invasion (p=0.01) and microscopic clusters of undifferentiated cancer cells ahead of the invasive front of the tumour ("budding", p=0.02). The same study also showed a statistically significant difference in the prevalence of lymph node metastasis according to the primary tumour localisation (Colon: 4; Rectum 10 p=0.03) (4). One study which analysed 76 T1 colorectal carcinomas from surgically resected Japanese patients, showed that in the univariate analysis tumour budding and a poor grade of differentiation were associated with lymph node metastasis (p=0.026; p=0.024) while multivariate analysis demonstrated that the actual number of tumour budding units alone was an independent prognostic factor for lymph node metastasis (6). Sakuragi et al. analysing 278 cases of T1 stage colorectal cancer resected using endoscopic resection or bowel surgery showed that a partial differentiation, a lymphatic channel invasion, a venous invasion and the presence of tumour budding were significant adverse prognostic factors in the univariate analysis (p<0.001) (7). In this study, the site of the primary tumour did not have any significant influence on lymph node metastasis rates. In another Japanese study the authors collected data on 292 early invasive colorectal adenocarcinomas from 285 consecutive patients from pathologic, endoscopic, or clinical records in order to obtain the indicators of nodal involvement and insufficient excision (8). Vascular invasion and tumour budding were reported to significantly affect the incidence of lymph node metastasis (p<0.0001) and to have an independent impact on nodal involvement. Finally a retrospective review of specimens by an independent pathologist blinded to the patients' clinical data conducted in Taipei on 159 patients undergoing curative resection of T1 adenocarcinoma showed that lymphatic vessel invasion (p=0.023) and budding (p=0.022) at the invasive front were independent risk factors of lymph node metastasis but did not statistically influenced 5-year overall survival rate. (10)

Local recurrence

A prospective cohort study of patients (n=192) included in the RCT Southwest Oncology Group 9041 Calcium Chemoprevention trial showed that site of primary cancer and whether the cancer was confined to a polyp were not significantly associated with differences in adenoma recurrence rates (2). Two prognostic factor correlation studies (5, 9) and a case-control study (11) investigated the incidence of local recurrence after curative resection of colorectal cancer and its correlation with tumour site and pathologic features. Only one study with a prospective design was retrieved (5), which analysed the prognostic factors for recurrence and the need for reoperation in 120 pT1 early rectal carcinoma patients who underwent local excision of rectal tumours. No definite correlation between the risk of recurrence and pathologic features was observed. Patients with critical resection margin and high-risk carcinomas (poorly to undifferentiated carcinomas and/or tumours with lymphatic or venous invasion), tumour extending to the resection margin (≤1 mm), or in the presence of tumour fragmentation) benefited from immediate reoperation, leading to a significant improvement (p=0.015) of the ten-year cancer-free survival rate. An American study performed on 1,031 patients with a curative resection for colonic adenocarcinoma with a medium follow-up of 69 months (range 2-212) showed that a poor differentiation was associated with a significantly greater incidence of local recurrence (15.8% vs. 1.1%; p=0.0011). No particular site of colonic cancer was significantly more prone to local recurrence (p=0.23) (9). This trend was also observed by Kramer et al. in a case control study aimed to compare clinical and pathologic features of recurrent colorectal cancer patients (n=357) and nonrecurrent colorectal carcinoma (n=1,731) and to analyse patterns of tumour recurrence (11). The site of the primary tumour did not have any significant influence on either local or metastatic recurrence rates.

Two of the retrieved studies reported relevant data for part 2 of this issue (4,7). Results are listed in Table 2. The PV for lymph node metastasis of budding alone was not superior to that of lymphovascular invasion alone. However, the combination of lymphovascular invasion and budding predicted lymph node metastasis in pT1 or pT2 tumours more accurately than lymphovascular invasion alone (4).

CONCLUSIONS

The included studies failed to demonstrate a statistically significant difference in adenoma/carcinoma recurrence rate when analysed by the site of primary tumour or whether the cancer was confined to a polyp. On the other hand, one study reported that the incidence of lymph node metastasis was significantly higher in rectal than in colonic tumours (4). With regard to the correlation between clinical outcomes and tumour pathologic features (poor grade of histologic differentiation, tumour budding, venous and lymphatic invasion) a clear indication of an increased risk of residual disease, lymph node metastasis, hematogenous metastasis, and mortality in poorly differentiated tumours was observed after endoscopic polypectomy or surgically resection (LEVEL OF EVIDENCE III/V). Other pathologic features, such as tumour budding, lymphatic and venous invasion appeared as possible adverse prognostic factor for lymph node metastasis but a clear guideline cannot be drawn as this correlation was not statistically significant in all studies. No information on the prognostic value of a partial excision was retrieved (LEVEL OF EVIDENCE III/V).

In these studies very few data were available to address the issue of the levels of reliability and diagnostic reproducibility of these pathologic features (LEVEL OF EVIDENCE-PART 2-III/V).

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Table 1. Summary of the main findings of the included studies

	Study design	Number of Patients	Considered Outcome	Site of primary tumour	Incomplete excision	Lymphatic vessel invasion	Blood vessel invasion	Poor Differentiation	Budding
Hassan 2005 (malignant polyps)	Systematic review	1900	1) residual disease 2) recurrent disease 3) lymph node metastasis 4) hematogenous metastasis 5) mortality	n.a.	n.a.	n.a.	1) no 2) n.a 3) yes 4) no 5) no	1) yes 2) n.a 3) yes 4) yes 5) yes	n.a.
Chu 2003 (colorectal cancer)	Cohort study	220	Recurrence	no	n.a	n.a.	n.a.	n.a.	n.a.
Blumberg 1999 (early rectal cancer)	Prognostic factor correlation study (cross-sectional)	159	Lymph node metastasis	n.a.	n.a.	no	yes	no	n.a
Okuyama 2002 (colorectal cancer)	Prognostic factor correlation study (cross-sectional)	101	Lymph node metastasis	yes rectum higher incidence	n.a.	yes	yes	n.a.	yes
Borschitz 2006 (early rectal cancer)	Prognostic factor correlation study (prospective cohort)	120	Local recurrence	no	n.a	n.a.	n.a.	n.a.	n.a.
Masaki 2006 (colorectal cancer)	Prognostic factor correlation study (cross-sectional)	76	Lymph node metastasis	n.a	n.a	no	no	yes	yes
Sakuragi 2003	Prognostic factor	278	Lymph node metastasis	no	n.a.	yes	yes	yes	yes

	Study design	Number of Patients	Considered Outcome	Site of primary tumour	Incomplete excision	Lymphatic vessel invasion	Blood vessel invasion	Poor Differentiation	Budding
(colorectal cancer)	correlation study (retrospective cohort)								
Ueno 2004 (colorectal cancer)	Prognostic factor correlation study (cross-sectional)	292	Lymph node metastasis	**n.a.**	**n.a.**	**n.a.**	**yes**	**n.a**	**yes**
Harris 2002 (colorectal cancer)	Prognostic factor correlation study (retrospective cohort)	1031	Local recurrence	**no**	**n.a**	**n.a**	**n.a**	**yes**	**no**
Wang 2005 (colorectal cancer)	Prognostic factor correlation study (retrospective cohort)	159	Lymph node metastasis	**n.a.**	**n.a.**	**yes**	**no**	**yes**	**yes**
Kraemer 2001 (colorectal cancer)	Prognostic factor correlation study (case-control)	2088	Recurrence	**no**	**n.a.**	**n.a.**	**n.a.**	**yes (only for rectum)**	**n.a.**

Notes:

Yes: a statistically significant correlation between the pathologic feature and the considered outcome was observed in a univariate analysis;

No: a statistically significant correlation between the pathologic feature and the considered outcome was not observed;

n.a.: not assessed

Table 2: diagnostic accuracy data

	Study design	Number of Patients	Considered Outcome	Prognostic factor	PPV	NPV	Specificity	Sensitivity	Diagnostic accuracy
Okuyama 2002 (colorectal cancer)	Prognostic factor correlation study (prospective cohort)	101	Lymph node metastasis	1) Lymphovascular invasion, 2) Budding, 3) Lymphovascular invasion or budding, 4) Lymphovascular invasion and budding	1) 34% 2) 24% 3) 24% 4) 39%	1) 96% 2) 93% 3) 98% 4) 92%	1) 76% 2) 63% 3) 52% 4) 84%	1) 79% 2) 71% 3) 93% 4) 57%	1) 76% 2) 64% 3) 58% 4) 80%
Sakuragi 2003 (colorectal cancer)	Prognostic factor correlation study (retrospective cohort)	278	Lymph node metastasis	depth ≥2000 µm and lymphatic invasion	15.6%	100%	55.6%	100%	n.a

7.5.2 Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Hassan 2005	Systematic review	To evaluate any association between the proposed histologic risk factors and the occurrence of unfavorable outcomes in patients with invasive malignant polyps.	31 retrospective studies included published between January 1980/June 2003; 1900 patients with diagnosis of invasive malignant polyps	Histological risk factor	1) residual disease 2) recurrent disease 3) lymph node metastasis 4) hemato-genous metastasis 5) mortality	***Residual disease according to*** <u>Margin of resection</u> Positive 55/181 (30.4%) p<0.05 Negative 4/142 (2.8%) Odds ratio: 15; 95% CI 5.3–42.7 <u>Poor differentiation</u> Positive 10/56 (17.8%) Negative 29/324 (9%) Odds ratio: 2.2; 95% CI 1–4.8 <u>Vascular Invasion</u> Positive 6/34 (17.6%) Negative 17/111 (15.3%) Odds ratio: 1.2; 95% CI 0.4–3.3 ***Recurrent disease according to*** <u>Margin of resection</u> Positive 13/77 (16.8%) p<0.05 Negative 4/357 (1.12%) Odds ratio: 17.9; 95% CI 5.7–56.7 <u>Poor differentiation</u> Data not reported <u>Vascular Invasion</u> Data not reported ***Lymph node metastasis according to*** <u>Margin of resection</u> Positive 13/181 (7.2%) Negative 13/142 (9.2%) Odds ratio: 0.8; 95% CI 0.3–1.7 <u>Poor differentiation</u> Positive 13/56 (23.2%) p<0.05 Negative 23/324 (7.1%) Odds ratio: 3.9; 95% CI 1.9–8.4 <u>Vascular Invasion</u> Positive 12/34 (35.3%) p<0.05 Negative 8/111 (7.2%) Odds ratio: 7; 95% CI 2.6–19.2	**III** The analysis showed that the different histological risk factors are clearly linked with clinical outcomes. A positive resection margin is largely predictive of local disease, the presence of poorly differentiated carcinoma is mainly associated with a higher cancer-related mortality, and vascular invasion with a higher risk of lymph node metastasis. These observations clearly suggest that after endoscopic polypectomy all three risk factors need to be simultaneously evaluated by the pathologist.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Hematogenous Metastasis according to Margin of resection Positive 30/325 (9.2%) p<0.05 Negative 8/655 (1.2%) Odds ratio: 8.2; 95% CI 3.7–18.2 Poor differentiation Positive 11/14 (9.6%) p<0.05 Negative 40/1520 (2.6%) Odds ratio: 3.9; 95% CI 2–7.9 Vascular Invasion Positive 13/250 (5.2%) Negative 38/1279 (3.0%) Odds ratio: 1.8; 95% CI 0.9–3.4 ***Mortality according to*** Margin of resection Positive 26/325 (8.0%) p<0.05 Negative 9/655 (1.4%) Odds ratio: 6.2; 95% CI 2.9–13.5 Poor differentiation Positive 14/96 (14.6%) p<0.05 Negative 27/1487 (1.8%) Odds ratio: 9.2; 95% CI 4.7–18.3 Vascular Invasion Positive 7/210 (3.3%) Negative 28/1194 (2.3%) Odds ratio: 1.4; 95% CI 0.6–3.3	

Definitions:

The status of the resection margin was defined as positive when regarded as positive or doubtful in each study and negative when a cancer-free edge of the submucosal transsection point was reported.

Differentiation of carcinoma was graded as well/moderate and poor according to the presence or absence of areas of poor differentiation.

Vascular invasion was taken as positive when presence of cancer in lymphatic channels or venous vessels was stated, and it was defined as negative when cancer invasion of these structures was clearly excluded.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE, HAND SEARCH OF RELATED BIBLIOGRAPHY
	Date restriction	January 1980/June 2003
	any restriction	Full paper publication, English language
Selection	Inclusion and exclusion criteria	Studies dealing with patients described as having a diagnosis of malignant polyp—defined as infiltration of malignant cells into the submucosa of an adenomatous polyp—and when at least one of the following histologic findings was clearly reported: 1) carcinoma in correspondence of the resection margin after endoscopic polypectomy, 2) poor differentiation of the invasive adenocarcinoma, and 3) vascular invasion. Studies enrolling patients with flat or depressed early colorectal cancer or when the number of treated and cured patients could not be extracted were excluded.
Validity assessment	Criteria and process used	Validity assessment of primary studies not described
Data abstraction	Process used	Double check of abstract and data collection
Quantitative data synthesis	Measures of effect, method of combining results	Chi-squared test and Fisher exact test as appropriate. Odds ratios and relative 95 percent confidence intervals also were calculated. Differences were considered significant at 5% probability level.
Results Trial flows	Trial flow and reason for exclusion	Flow charts were not reported; number and reasons of excluded studies were reported.
Study characteristics	Type of studies, participants, interventions, outcomes	Not reported
Study results	Descriptive data for each trial	Not reported
Methodological quality	Summary description of results	Yes, by outcome not by study
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Pooling of data was performed

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Chu 2003	Prospective cohort study of patients included in the randomised controlled trial Southwest Oncology Group 9041 Calcium chemoprevention trial USA	192 patients with colorectal cancer stage 0 (5%), I (52%), II (43%), Cancer confined to polyps (24%). Not specified how many patients had an endoscopical removal of cancer	Incidence of neoplasia at follow up examinations basing on baseline findings	3 years	***Overall neoplasia recurrence rate***: 31% ***Adenoma recurrence rate by stage*** Stage 0: 37% Stage I: 24% Stage II: 39%. ***Adenoma recurrence rate by site a baseline:*** Colon (154): 32% Rectum (38):29% Confined to polyp (46) : 24% No confined to polyp (146): 34% Site of the adenoma recurrence: Cecum: 17% Ascending colon: 21% Transverse colon : 19% Left and sigmoid: 10% Rectum 25% Both rectum and proximal: 8%	**III** There was not a statistically significant difference in adenoma recurrence rate when analysed by sex, age, site or whether the cancer was confined to a polyp.

Quality assessment: Population truly representative of the population at average risk. Non exposed cohort drawn form the same community as the exposed cohort Ascertainment of exposure by clinical records. Assessment of outcome by record linkage. Subjects lost to follow 12.8%; description provided of those lost.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Blumberg 1996	Prognostic factor correlation study (cross-sectional)	To define the frequency of lymph node metastasis in small T1 and T2 rectal cancers technically amenable to local excision and to determine if standard histo-pathologic features of the primary tumour are useful in stratifying the risk of lymph node metastasis	159 patients (48 T1, 111 T2) with localized rectal tumours technically amenable to local excision not receiving preoperative radiotherapy Median age: 62 (29-85) years; 79 females "High risk" patient: presence of blood vessel invasion, lymphatic vessel invasion, or poor differentiation. USA	Local excision	Correlation between the following pathologic features and the presence of regional lymph node metastasis: • Extent of transmural invasion • Blood vessel invasion • Lymphatic vessel invasion • Tumour size • Tumour differentiation	***Regional lymph node metastasis*** Overall: 24/159 (15%) ***Lymph node metastasis according to:*** T stage T1: 5/48 (10%) T2: 19/111 (17%) RR: 1.7; p=0.28 Size ≤3 cm: 16/110 (15%) >3 cm: 8/49 (16%) RR: 1.1; p=0.77 Differentiation Well: 2/9 (22%) Moderate: 19/140 (14%) Poor 3/10 (30%) RR: 2; p=0.18 Lymphatic vessel invasion Negative 22/153 (14%) Positive 2/6 (33%) RR: 2.3; p=0.2 Blood vessel invasion Negative 19/144 (13%) Positive 5/15 (33%) RR: 2.5; p=0.04 ***Lymph node Metastasis according to Risk stratification*** ***All patients:*** "High risk" (n=29): 9 (31%) "Low risk" (n=130): 15 (11%) p=0.008 ***T1 patients:*** "High risk" (n=6): 2 (33%) "Low risk" (n=42): 3 (7%) p=0.04	**V** Tumours with blood vessel invasion had a significantly (p=0.04) increased (2.5-fold higher) risk of lymph node metastasis compared with tumours without blood vessel invasion. Tumours with more advanced T stage (T2), lymphatic vessel invasion, or poor differentiation had a higher likelihood (p=not significant) of regional lymph node metastasis. The risk stratification analysis showed that the presence of blood vessel invasion, lymphatic vessel invasion, or poor differentiation in the primary tumour, identifies a population with a significantly higher risk of lymph node metastasis.

Quality assessment: prospective recruitment; adequate representativeness of the selected cohort; comparability of cohorts on the basis of the analysis (other than prognostic factors) not clear as no adjustment was performed; adequate description of the outcome assessment.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Okuyama 2002	Prognostic factor correlation study (cross-sectional)	1. to examine budding in pT1 or pT2 well-differentiated colorectal carcinomas; 2. to correlate budding with other clinical and pathologic characteristics; 3. to explore whether the combination of lymphovascular invasion and budding* has superior predictive value in lymph node metastasis to that of lymphovascular invasion or budding alone.	101 pT1 or pT2 well-differentiated colorectal adenocarcinom as extracted from 504 colorectal carcinomas curatively resected Mean age 61 (37-85) years 57 male Japan	-	Prevalence of budding Prevalence of lymph node metastasis on the basis of the presence of the following pathologic features: • Tumour location • Tumour size • Depth of invasion • Lymphatic invasion • Venous invasion • Budding Predictive value (PV) of budding, lymphovascular invasion, and their combination for lymph node metastasis	**Prevalence of Budding according to** Depth of invasion Submucosa (pT1): 10; Muscularis propria (pT2): 32; p=0.007 Lymphatic invasion Present: 20; Absent: 22; p=0.002 **Prevalence of lymph node metastasis according to** Location Colon: 4; Rectum 10 p=0.03 Lymphatic invasion Present: 11; Absent: 3; p<0.0001 Venous invasion Present: 3; Absent: 11; p=0.01 Budding Present: 10; Absent: 4; p=0.02 **Diagnostic accuracy for lymph node metastasis** Lymphovascular invasion Positive lymph node: 11 Sensitivity: 79% Specificity: 76% Positive PV: 34% Negative PV: 96% Diagnostic accuracy: 76% Budding Positive lymph node: 10 Sensitivity: 71% Specificity: 63% Positive PV: 24% Negative PV: 93% Diagnostic accuracy: 64%	V The prevalence of lymph node metastasis was significantly higher in rectal than in colonic tumours and in tumours having lymphatic or blood vessel invasion and budding. The PV for lymph node metastasis of budding alone was not superior to that of lymphovascular invasion alone. However, the combination of lymphovascular invasion and budding predicted lymph node metastasis in pT1 or pT2 tumours more accurately than lymphovascular invasion alone.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Lymphovascular invasion or budding Positive lymph node: 13 Sensitivity: 93% Specificity: 52% Positive PV: 24% Negative PV: 98% Diagnostic accuracy: 58% Lymphovascular invasion and budding Positive lymph node: 8 Sensitivity: 57% Specificity: 84% Positive PV: 39% Negative PV: 92% Diagnostic accuracy: 80%	

* microscopic clusters of undifferentiated cancer cells ahead of the invasive front of the tumour

Quality assessment: Prospective recruitment, adequate representativeness of the selected cohort; adequate comparability of cohorts on the basis of the design or analysis; adequate description of the outcome assessment.

Author, publication year	Study design	Objective	Participants	Follow up	Intervention	Outcome	Results	Level of evidence Conclusions
Borschitz 2006	Prognostic factor correlation study (prospective cohort)	To determine prognostic factors for recurrence and the need for reoperation	120 pT1 early rectal carcinoma patients underwent local excision of rectal tumours 64 males Mean age 68 (39-89) years Data available for 105 patients (89%) GROUP A: "low-risk" cancer after clear R0 resection GROUP B: cases with R1 resection, "high risk" carcinomas (poorly to undifferentiated carcinomas and/or tumours with lymphatic or venous invasion), tumour extending to the resection margin (≤1 mm), or in the presence of tumour fragmentation. Germany	74 (6-211) months	Local resection of pT1 rectal carcinoma using transanal endoscopic microsurgery technique (TEM)	Local recurrences in dependence on: • tumour stage • tumour size • localisation (anterior, posterior, or lateral wall) • distance from the ano-cutaneous line (upper, middle, lower rectum) • extent of resection (full thickness/partial wall) • quality of the resection margin Cancer free survival	***Local Recurrence according to*** <u>Third of rectum (cm)</u> 4-8: 6/33 (18%) 8-12: 2/28 (7%) >12: 3/23 (13%) p=0.47 <u>Location</u> Anterior wall: 4/27 (15%) Posterior wall: 4/32 (13%) Lateral wall: 3/25 (12%) p = 0.97 <u>Extent Resection</u> Full-thickness: 4/50 (8%) Partial wall: 7/34 (21%) p=0.15 <u>Tumour size</u> ≤3 cm: 4/48 (8%) >3-≤6 cm: 6/32 (19%) >6 cm: 1/4 (25%) p=0.27 ***Cancer free survival*** <u>Group A:</u> TEM resection (n=66): 5-yrs 94%; 10-yrs 89% TEM + reoperation (n=4) 5-yrs 75%; 10-yrs 75% p=0.162 <u>Group B</u>: TEM resection (n=18) 5-yrs 57%; 10-yrs 49% TEM + reoperation (n=17) 5-yrs 93%; 10-yrs 93% p= 0.015	**III** No definite correlation between the risk of recurrence and tumour localisation, tumour size was observed. The lowest recurrence rate was achieved after a full-thickness excision compared to a partial wall excision but this difference was not statistically significant. Patients with critical resection margin and high-risk carcinomas benefited from immediate reoperation, leading to a significant improvement (p=0.015) of the ten-year cancer-free survival rate.

Quality assessment: prospective design; adequate representativeness of the selected cohort; comparability of cohorts on the basis of the analysis (other than prognostic factors) not clear as no adjustment was performed; adequate description of the outcome assessment; follow up clearly reported but no information on the patients lost at follow up.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Masaki 2006	Prognostic factor correlation study (cross-sectional)	to construct a formula to predict the risk of lymph node metastasis in T1 colorectal carcinomas using the actual number of budding tumour cells *per se* and to determine the indication for additional surgery after endoscopic mucosal resection of T1 colorectal carcinoma using decision analysis.	76 T1 colorectal carcinomas surgically resected patients; 51 men and 24 women Mean age 68 years (range 40-87) Japan	-	Number of budding and lymph node metastasis on the basis of: • predominant grade, • lymphatic vessel invasion, • blood vessel invasion, • regional lymph node involvement, • degree of submucosal invasion, • surgical margin status, • adenomatous component, • dedifferentiated histology at the invasive margin • tumour budding*	***Number of budding according to*** Histology Well (n=61): 9±1 Moderate (n=10): 16±6 Poor (n=3): 20±15 p=0.285 Lymphatic invasion Positive (n=13): 17±5 Negative (n=60): 8±1 p=0.165 Venous invasion Positive (n=13): 15±4 Negative (n=60): 9±2 p=0.075 Vascular invasion Positive (n=24): 15±3 Negative (n=49): 7±1 p=0.028 relative grading of the depth of submucosal invasion Level 1 (n = 14): 9±4 Level 2 (n = 18): 12±4 Level 3 (n = 41): 11±2 p=0.568 abs grading of the depth of submucosal invasion sm1 (n = 8): 1±1 sm2 (n = 2): 13±7 sm3 (n = 64): 11±2 p=0.011 absolute grading of the width of submucosal invasion sma (n = 6): 0±0 smb (n = 8): 11±4 smc (n = 60): 11±2 p=0.010	V In the univariate analysis tumour budding and a poor grade of differentiation were associated with lymph node metastasis. Multivariate analysis showed that only the actual number of tumour budding units alone was an independent prognostic factor for lymph node metastasis. No significant association between lymph node metastasis and lymphatic invasion, venous invasion, relative or absolute grades of the depth of invasion or absolute grade of the width of invasion (p=0.619) was observed.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Lymph node metastasis according to <u>Poor grade of differentiation</u> Positive LNM: 1 Negative LNM: 2 p=0.024 <u>Positive lymphatic invasion</u> Positive LNM: 2 Negative LNM: 11 p=0.172 <u>Positive venous invasion</u> Positive LNM: 0 Negative LNM: 13 p=0.369 <u>Number of budding</u> Positive LNM: 26±10 Negative LNM: 9±1 p=0.026	

* tumour budding: the finding of a single cancer cell or a solitary trabecular form along the entire invasive margin.

Quality assessment: retrospective recruitment; representativeness of the selected cohort cannot be established; comparability of cohorts on the basis of the analysis (other than prognostic factors) not clear as no adjustment was performed; adequate description of the outcome assessment.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Sakuragi 2003	Prognostic factor correlation study (retrospective cohort)	To select appropriate treatment for T1 stage colorectal cancers analyse on the basis of the depth of submucosal invasion and other histologic factors.	278 cases of T1 stage colorectal cancer resected using endoscopic resection or bowel surgery retrospectively analysed Medium age, 61.9±10.5 years; 175 male "no lymph node metastasis": no recurrence occurred during two years or more after endoscopic resection Japan	-	Incidence of lymph node metastasis on the basis of the presence of the following pathologic features: • Depth of submucosal invasion • Histologic differentiation • Histology of invasive front (budding) • Lymphatic invasion • Venous invasion • Adenoma component • Tumour location • Tumour size Predictive factor for lymph node metastasis	***Incidence of lymph node metastasis according to*** <u>Location</u> Right Colon (cecum, ascending colon, transverse colon): 6.3%; Left colon (descending colon and sigmoid colon): 7.6%; Rectum: 8.3% $p=0.9$ <u>Differentiation</u> Well: 8 (3.4%); Other: 13 (32.5%); $p<0.001$ <u>Lymphatic invasion</u> Present: 19 (34.5%); Absent: 2 (0.9%); $p<0.001$ <u>Venous invasion</u> Present: 5 (20.8%); Absent: 16 (6.3%); $p=0.025$ <u>Poor differentiation in the invasion front (budding)</u> Present: 16 (21.1%); Absent: 5 (2.5%); $p<0.001$ <u>Depth</u> <2000 µm: 1 (0.7%); ≥2000 µm: 18 (15.5%); not measurable: 2 (10.0%); $p<0.001$ ***Odds ratio of lymph node metastasis for predictive factors according to*** <u>Depth ≥2000 µm:</u> OR 13.1 (95% CI 1.5-117.4); $p=0.022$ <u>Lymphatic invasion</u> OR 25.6 (95% CI 5.0-131.0); $p=0.0001$ ***Predictive factors (depth ≥2000 µm and lymphatic invasion) and lymph node metastasis*** one or both risk factors: 135 (48.6%) lymph node metastasis: 21/135 (15.6%). sensitivity: 100%; specificity: 55.6%; positive predictive value: 15.6%; negative predictive value: 100%	III A relationship between the measured depth and the probability of lymph node metastasis has been demonstrated. Lymphatic channel invasion appeared a significant adverse prognostic factor in both uni- and multivariate analysis while poor differentiation in the invasion front (budding) was a significant factor for the prediction of lymph node metastasis only in the univariate analysis.

Quality assessment: retrospective design, adequate representativeness of the selected cohort; adequate comparability of cohorts on the basis of the design or analysis; adequate description of the outcome assessment; follow up not reported.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Ueno 2004	Prognostic factor correlation study (cross-sectional)	To determine the criteria for a conservative approach in patients with local excision of early invasive colorectal cancer.	292 early invasive colorectal adenocarcinomas from 285 consecutive patients median age 62 (32–91); ratio of women to men was 1:1.5 Japan	Data on early invasive colorectal cancers were collected from pathologic, endoscopic, or clinical records to obtain the indicators of nodal involvement and insufficient excision	Prevalence of lymph node metastasis on the basis of the presence of the following pathologic features: • Haggitt's classification, • width and depth of submucosal invasion, • type of growth pattern (polypoid growth/ nonpolypoid growth), • presence or absence of a depression zone, • adenoma component, • mucin-producing, • cribriform formation, • tumour grade, • vascular invasion (definite cancer involvement of lymphatic vessels and/or venous vessels), • tumour budding	***Prevalence of lymph node metastasis*** ***Overall*** 33/251 (13.1%) ***Nodal involvement according to:*** Tumour grade Favorable: 10 (5.7%) Unfavorable: 23 (29.2%) OR (univariate analysis): 7.3 (95% CI 3.3–16.4) p<0.0001 OR (multivariate analysis): 2.9 (95% CI 1.2–7.4) p=0.023 Vascular invasion Absence: 10 (5.7%) Presence: 23 (30.7%) OR (univariate analysis): 7.3 (95% CI 3.3–16.4) p<0.0001 OR (multivariate analysis): 2.7 (95% CI 1.1–7.0) p=0.039 Cribriform pattern Absence: 14 (7.3%) Presence: 19 (32.2%) OR (univariate analysis): 6.0 (95% CI 2.8–13.1) p<0.0001 OR (multivariate analysis): 3.9 (95% CI 1.6–9.4) p=0.002 Tumour budding Negative: 17 (8.0%) Positive: 16 (42.1%) OR (univariate analysis): 8.4 (95% CI 3.7–18.9) p<0.0001 OR (multivariate analysis): 3.7 (95% CI 1.4–9.9) p=0.008	V The prevalence of nodal involvement was significantly affected by the following histologic parameters: cribriform formation, tumour grade, vascular invasion, and tumour budding. Multivariate logistic analysis showed that these parameters have an independent impact on nodal involvement.

Quality assessment: retrospective recruitment, adequate representativeness of the selected cohort; adequate comparability of cohorts on the basis of the design or analysis; adequate description of the outcome assessment.

Author, publication year	Study design	Objective	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Harris 2002	Prognostic factor correlation study (retrospective cohort)	To determine the incidence of local recurrence after curative resection of colorectal cancer	1,031 patients with a curative resection for colonic adenocarcinoma. USA	Medium follow up 69 (range 2-212) months	Incidence of local recurrence	***Incidence of local recurrence*** 32/1073 (3.1%) Purely local: 18 (1.7%) Combined with distant: 14 (1,4%) ***Crude mean survival*** Purely local: 14 (range, 1–62) months. Combined with distant: 12 (range, 1–46) months. No particular ***site of colon cancer*** that was significantly more prone to LR (p=0.23) ***Number of tumour/number of local recurrence*** Tumour differentiation Well: 115 (11.2%); recurrence 0 (0%) Moderate: 750 (73%); recurrence 21 (2%) Poor: 162 (15.8%); recurrence 11 (1.1%) p=0.0011 (well/moderate vs. poor)	**III** Poorly differentiated tumours had a significantly greater incidence of local recurrence than those of a more favourable morphologic and histologic grade.

Quality assessment: retrospective design; adequate representativeness of the selected cohort; comparability of cohorts on the basis of the analysis (other than prognostic factors) not clear as no adjustment was performed; adequate description of the outcome assessment.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Wang 2005	Prognostic factor correlation study (retrospective cohort)	To analysed the features of T1 colorectal carcinoma and to determine risk factors of lymph node metastasis and their impact on long-term survival	159 patients undergoing curative resection of T1 adenocarcinoma 107 males; mean age at surgery 64.9±12.3 (range 18-89) Taipei	Retrospective review of specimens by an independent pathologist blinded to the patients' clinical data	Association between lymph node metastasis and clinicopatho logical features. Overall survival	***Patient data*** Mean number of retrieved lymph nodes: 9.4±7.8 (range 2-37); Lymph node metastasis: 16/159 (10.1%) Overall survival (mean follow up: 61.8±54.2, range 1-234 months): 143/159 (90%) ***Clinicopathologic features according to lymph node status*** Mean size of tumour T1N0: 2.3±1.3 cm T1N1or2: 2.8±1.8 cm p=0.103 Poor grade of differentiation T1N0: 1 T1N1or2: 6 p=0.005 Presence of blood vessel invasion: T1N0: 1 T1N1or2: 1 n.s. Presence of lymphatic vessel invasion: T1N0: 4 T1N1or2: 7 p=0.023 Presence of tumour budding: T1N0: 13 T1N1or2: 11 p=0.022 ***5-year overall survival rate according to*** Grade Well 49.96 Moderately 33.04 Poorly 28.57 Univariate p=0.0025 Multivariate p=0.303	**III** This study showed that histology grade, lymphatic vessel invasion, and budding at the invasive front were independent risk factors of lymph node metastasis. However, the long-term survival was statistically influenced only by age and by the number of total sampling nodes and not by the risk factor of lymph node metastasis.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Blood vessel invasion Absent 37.64 Present 0 Univariate p=0.711 Lymphatic vessel invasion Absent 38.92 Present 10.91 Univariate p=0.5163 Lymph node metastasis absent 36.91 present 36.46 Univariate p=0.6245 Budding Absent 35.08 Present 48.89 Univariate p=0.5273	

Quality assessment: retrospective design, blinded assessment of outcome.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Kraemer 2001	Case control risk factor study	To compare clinical and pathologic features of recurrent and nonrecurrent colorectal carcinoma and to analyse patterns of tumour recurrence in the setting of a specialized department of colorectal surgery to enable us to stratify risk factors following surgery.	1,731 non-recurrent colorectal cancer patients (821 colon, 910 rectum) and 357 recurrent colorectal cancer patients (164 colon, 193 rectum) following potentially curative surgery Singapore	Case: recurrent colorectal cancer patients; Control: non-recurrent colorectal cancer patients	Clinical and pathologic features of recurrent and nonrecurrent colorectal carcinoma	recurrent disease ***local recurrences*** 47/357 ***distant metastases*** 236/357 ***both*** 74/357 ***Risk factor for recurrence (median follow up 61 months, n=1499)*** Invasion of adjacent tissue: Rectum OR 0.16; 95% CI 0.08-0.31 p<0.0001 Colon OR 0.58; 95% CI 0.36-0.95 p=0.0384 Fixation to adjacent tissue: Rectum OR 0.36; 95% CI 0.22-0.57 p<0.0001 Colon n.s. Tumour grading: Rectum: poor vs. moderate/well OR 0.34; 95% CI 0.20-0.58 p<0.0001 Colon: poor vs. moderate/well n.s. Tumour site: Individual site vs. remaining colon: n.s. Dukes classification: "C" vs "B" OR 0.35; 95% CI 0.27-0.46 p <0.0001 "C" vs. "A" OR 0.12; 95% CI 0.07-0.21 p<0.0001 "B" vs. "A" OR 0.34; 95% CI 0.19-0.62 p <0.0002 Rectum: "C" vs. "A/B 0.26; 95% CI 0.18-0.39 p <0.0001 Colon: "C" vs. "A/B" 0.54; 95% CI 0.40-0.72 p <0.0001	**IV** The site of the primary tumour did not have any significant influence on either local or metastatic recurrence rates

Quality assessment: matching not performed as the study was aimed to compare pathologic features of the two groups and evaluate their impact as risk factor for recurrence. Population not only T1.

7.6 Impact of external quality assurance programmes on the variability of reporting of pathology of colorectal, breast and other tumours

7.6.1 Summary document

Rita Banzi and Silvia Minozzi

CLINICAL QUESTION 7

What is the evidence that external quality assurance programmes decrease the variability of reporting of pathology in
- colorectal cancer
- breast cancer
- other tumours

PICOS

P: All patients with a) colorectal cancer b) breast cancer c) other tumours
I: External quality programmes
C: Not applicable
O: Optimal prognosis / mortality / recurrence rate
S: (Systematic reviews of) diagnostic accuracy; cross-sectional studies, case series

SEARCH METHOD

We searched MedLine databases from 1998 using the following search strategy:
tumour OR tumours OR tumour OR tumours OR cancer OR cancers OR neoplasm OR neoplasms
AND external quality programme OR external quality test* OR external quality programmes OR external quality programs OR external quality program

We also searched the Cochrane Library and retrieved additional papers from the analysis of the quoted bibliography.

RESULTS

We were unable to retrieve relevant publications on external quality assurance (EQA) programmes for colorectal cancer screening and diagnosis. We found 4 cohort studies assessing the impact of EQA programmes in decreasing the diagnostic accuracy and variability in different oncologic settings. Two studies evaluated British national EQA programme for breast cancer (1) and head and neck cancer pathology (2) respectively. Two studies were Italian projects on the quality of cytologic diagnosis (3, 4).

The UK EQA programme in breast histopathology (UK National Health Service Breast Screening Programme, NHSBSP) was introduced in 1990 with the objective of improving the consistency of pathologists in reporting breast disease (1). For pathologists in particular, this required for the first time mandatory participation in an EQA scheme. Over 50 sets of 12 cases circulated to pathologists who report breast pathology in the UK over a 3-month period. The participating pathologists independently examined the slides and for each case completed a tick box proforma, which includes their opinion on the diagnosis. These completed proformas were returned to the cancer screening evaluation unit (Institute of Cancer Research, Sutton, UK) where the participants' opinions for each case were collated. This procedure is repeated twice a year. The performance profiles of pathologists were reported in a prospective cohort study which studied 10 circulations of 12 slides evaluated by 407-485 pathologists between 1998 and 2002.(1) The number of cases with a minimum of 80% agreement among coordinators was 109 out of 120. During the five year period of study, 11 of the 120 cases used in the EQA circulations did not achieve an 80% consensus among more than 400 participants. Individuals who perform less well in their first EQA improve in subsequent EQAs. Pathologists who joined the scheme improved over time, particularly those who did less well initially. The average score of pathologists who left the programme for any reasons tended to be slightly lower than that for non-leavers.

A British Head and Neck Histopathology EQA Scheme (HNS) was developed gradually from the Oral Pathology EQA Scheme (OMFS) and was evaluated in a cross-sectional study (2). This project was aimed at improving education and quality assurance (including the detection of sub-standard performance) in line with the recommendations of the Royal College of Pathologists. 11 circulations of 168 cases were evaluated by 22 oral pathologists and one ENT/general pathologist between 1999 and 2005. The considered outcome was the personal performance score (2 points for responses that are judged complete and correct; 1 for responses that are judged incomplete or deficient; 0 for responses judged to be wrong). In 68 (40%) of the 168 cases, all respondents scored 2 marks. In 23 cases (14%), at least one respondent scored 0. In 35 cases (21%), at least one respondent scored 1 mark. In 33 cases (20%), there was at least one 0 and at least one 1. The remaining nine cases (5%) were excluded from the scoring.

One Italian prospective cohort study investigated whether the participation in a pilot phase of an EQA programme on cervical cancer increases the reliability and accuracy of diagnosis in a second phase (3). The study consisted in the circulation of 40 slides examined by 14 laboratories and a subsequent discussion between representatives of laboratories and reassessment of the most controversial slides. The results of the second phase were similar to those of the first phase: no substantial improvement in accuracy and little reduction in variability were observed.

A retrospective cohort study explored the effectiveness of an Italian external Quality assessment scheme in classical cytogenetics which was launched in 2001 (4). This project was aimed at reaching a high standard of quality in the cytogenetic laboratories performance in prenatal, postnatal, and cancer cytogenetics. 58 cytogenetic public laboratories covering all Italian regions were enrolled on a voluntary basis between 2001 and 2004 and were asked to retrospectively send images of clinical cases and the corresponding written reports. The report reviewers blinded to the name of the laboratory assessed the images and reports and gave their feedback on performance and completeness of reporting. Regarding only oncologic cytogenetics, the number of clinical cases which were correctly analysed and interpreted and where no inaccuracy was detected increased from 18% in 2001 to 50% in 2004 (χ^2, p=0.073). Reports and/or images that could not be evaluated decreased by 24% from 2001 to 2004 (Fisher's exact text, p=0.024). Complete reports in oncological diagnosis increased significantly between 2001 and 2004 (p=0.008).

CONCLUSIONS

Drawing a conclusion on whether EQA assurance programmes decrease the variability of reporting of pathology in colorectal cancer and other tumours is difficult as little evidence regarding different EQA programmes was retrieved. We found no relevant publication on EQA programmes for colorectal

cancer screening and diagnosis. The conclusion of three out of four of the included study reports that the participation in interpretive histopathology schemes, as those offered by national EQA programmes, is an important part of histopathology practice, offering invaluable educational experience and an excellent opportunity to compare ones own knowledge and diagnostic expertise with a wide peer group. This could have a potential effect in improving diagnostic accuracy and consensus among pathologists. However, as three out of the four considered programmes enrolled centres on a volunteer basis, this could have resulted in selection of a specific type of pathologist (i.e. more prone to follow guidelines, etc.) thus affecting the applicability of the results to standard practice. (LEVEL OF EVIDENCE III/V)

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7.6.2   Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Parham 2006	External quality assurance programme in breast histopathology (UK National health Service Breast Screening Programme, NHSBSP) The original role of the National Health Service breast screening programme (pathology) external **Quality assessment** (EQA) scheme was educational; it aimed to raise standards, reinforce use of common terminology, and assess the consistency of pathology reporting.	Prospective study	10 circulation of 12 slides evaluated by 407-485 pathologists between 1998 and 2002 UK	Performance profiles of pathologists assessed using rank order and fifth percentile metho-dologies.	***Cases with a minimum of 80% agreement among coordinators*** 109/120 ***Number of circulation achieving an 80% consensus*** 11% circulation 2002(II); Nparticipants=478; 10% circulation 2002(I); Nparticipants=485; 12% circulation 2001(II); Nparticipants=467; 12% circulation 2001(I); Nparticipants=476; 10% circulation 2000(II); Nparticipants=466; 12% circulation 2000(I); Nparticipants=431; 9% circulation 1999(II); Nparticipants=470; 12% circulation 1999(I); Nparticipants=472; 10% circulation 1998(II); Nparticipants=464; 9% circulation 1998(I); Nparticipants=407. ***Mean improvement in score (% points)*** 2nd circulation (N=199): 0.16 (95% CI 20.8-1.11) 3rd circulation (N=152): 0.26 (95% CI 20.67-1.19) 4th (N=124): 1.02 (95% CI 0.83-3.0) 5th (N=99): 1.81 (95% CI 0.69-2.91) 6th (N=76): 1.09 (95% CI 20.18-2.36) 7th (N=52): 0.92 (95% CI 0.66-2.42) 8th (N=33): 1.0 (95% CI 20.92-2.92)	**III** During the five year period of study, 11 of the 120 cases used in the EQA circulations did not achieve an 80% consensus among more than 400 participants. Individuals who perform less well in their first EQA improve in subsequent EQAs. Pathologists who joined the scheme improved over time, particularly those who did less well initially. There was no obvious association between performance and the number of breast cancer cases reported each year. This is not unexpected because the EQA does not measure expertise, but was established to demonstrate a common level of performance (conformity to consensus) for routine cases, rather than the ability to diagnose unusual/difficult cases

*NST preferred term for tumours of no special type previously classified as ''ductal'

Quality assessment: National Health Service breast cancer screening programme (NHSBSP) external quality programme. Mandatory programme (centres involved can be representative of the general situation). Over 50 sets of 12 cases are circulated to pathologists in the UK who report breast pathology over a three month period. The participating pathologist independently examines the slides and for each case completes a tick box proforma, which includes their opinion on the diagnosis. These completed proformas are returned to the cancer screening evaluation unit (Institute of Cancer Research, Sutton, UK), where the participants' opinions for each case are collated. This procedure is repeated twice a year. An analysis of pathologists who leave the programme was also presented: the average score of leavers tended to be slightly lower than that for non-leavers.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Woolgar 2006	National Head and Neck Histopathology External Quality Assurance Scheme (HNS). Two circulations of 12 cases were sent out each year and members' responses were discussed at a review session.	Cross-sectional study	11 circulation of 168 cases evaluated by 22 oral pathologists and one ENT/general pathologist between 1999 and 2005 UK 168 cases submitted by 34 pathologists	Personal performance score: 2 for responses that are judged complete and correct; 1 for responses that are judged incomplete or deficient; 0 for responses judged to be wrong	All respondents scored 2 marks: 68/168 (40%) at least one respondent scored 0: 23/168 (14%) at least one respondent scored 1 mark: 35/168 (21%) at least one 0 and at least one 1: 33/168 (20%) The remaining nine cases (5%) were graded E and excluded from PPA scoring.	**V** The experiences of the HNS show that participation in an interpretive histopathology scheme is an important part of histopathology practice, offering invaluable educational experiences and an excellent opportunity to compare ones own knowledge and diagnostic expertise with a wide peer group. To gain maximum benefits, members must attend and participate in the review sessions.

Quality assessment: national external quality assurance programme aimed at improve education and quality assurance (including the detection of substandard performance) in line with the recommendations of the Royal College of Pathologists. Head and Neck Histopathology EQA Scheme (HNS) developed gradually from the Oral Pathology EQA Scheme (OMFS). Attendance rates ranged from 63% to 80% in the (OMFS) while attendance rates of only 44% to 56% have been achieved in the last five HNS circulations.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Branca 1998	External quality control programme of cervical cancer diagnosis: discussion between representatives of laboratories and reassessment of the most controversial slides	Prospective study	40 slides examined by 14 laboratories Italy	To assess whether participation in the first phase of the external quality control programme increases the reliability and accuracy of diagnosis in the second phase	*Adequacy* Gross agreement: 2nd phase 0.90; (1st phase: 0.85) K: 2nd phase 0.48 (95% CI 0.45-0.52); 1st phase: 0.32 *Diagnosis* Gross agreement: 2nd phase 0.64 (1st phase: 0.60) K: 2nd phase 0.50 (95% CI 0.48-0.52); 1st phase: 0.46 *Recommendations for treatment* Gross agreement: 2nd phase 0.55; (1st phase: 0.67) K: 2nd phase 0.35 (95% CI 0.32-0.38); 1st phase: 0.44 *Diagnostic difficulty* Gross agreement: 2nd phase 0.45 (1st phase: 0.47) K: 0.19 (95% CI 0.16-0.22); (1st phase: 0.13) *Diagnosis of LSIL (CIN 1 and HPV)* Sensitivity: 2nd phase 0.92 (1st phase: 0.61) Specificity: 2nd phase 0.97 (1st phase: 0.96) *Diagnosis of HSIL (CIN 2 and 3)* Sensitivity: 2nd phase 0.62 (1st phase: 0.76) Specificity: 2nd phase 0.89 (1st phase: 0.95)	**III** The results of the second phase are similar to those of the first phase: No substantial improvement in accuracy and little reduction in variability were observed.

Quality assessment: National EQA project, laboratories enrolled on a voluntary basis. Pathologists were asked during both phases to complete a standardised form. At the end of the circulation period each slides with diagnostic discrepancies were reviewed collectively; a representative of each laboratory attended the meetings and were asked to report back his/her colleagues to promote a debate on major discrepancies. Diagnostic classification criteria clearly reported.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Floridia 2008	Italian external **Quality assessment** scheme in classical cytogenetics supported by the Italian Ministry of Health. This project was aimed at reaching a high standard of quality in the cytogenetic laboratories performance in prenatal, postnatal, and cancer cytogenetics.	Retro-spective cohort study	58 cytogenetic public laboratories covering all Italian regions enrolled on a voluntary basis between 2001 and 2004 Italy	Participation and completeness of reporting (number of cultures established, analysed, number of metaphases, interpretation of findings).	***Overall Participation*** 58/121 laboratories (42% of the Italian laboratories performing cytogenetic analysis) ***Participation trend (all laboratories)*** 36 laboratories in 2001; 46 laboratories in 2002; 49 laboratories in 2003; 51 laboratories in 2004. <u>Oncological cytogenetics</u> ***% of complete reports (only oncological diagnosis)*** 2001 (n=17): 53% 2002 (n=24): 20.8% 2003 (n=25): 44% 2004 (n=24): 62.5% 2002 vs. 2004 p=0.008[*] ***% of incomplete reports (only oncological diagnosis)*** 2001 (n=17): 23.5% 2002 (n=24): 62.5% 2003 (n=25): 44% 2004 (n=24): 37.5% ***% of reports not evaluated (only oncological diagnosis)*** 2001 (n=17): 23.5% 2002 (n=24): 16.7% 2003 (n=25): 12% 2004 (n=24): 0% The number of oncologic clinical cases which were correctly analysed and interpreted and where no inaccuracy was detected increased from 18% in 2001 to 50% in 2004 (χ^2, p=0.073). Reports and/or images that could not be evaluated decreased by 24% from 2001 to 2004 (Fisher's exact text, p=0.024)	**III** Complete reports in oncological diagnosis increased significantly between 2001 and 2004. Participation in external **Quality assessment** programs has significant advantages, helping to standardize and to assure quality in cytogenetic testing

* comparison between 2001 and 2004 was not performed due to different parameter assessment.
Quality assessment: Laboratories are representative of all the Italian regions but the enrolment was on a voluntary basis; retrospective format: laboratories were asked to send images of clinical cases and the corresponding written reports; the reports reviewer was blinded to the name of the laboratory.

7.7 Impact of the minimum number of specimens reported in a screening programme

7.7.1 Summary document

Rita Banzi

CLINICAL QUESTION 8

Is there evidence for a minimum number of specimens that a pathologist should report in a screening programme for
- adenomas
- colorectal cancer resections

PICOS

P: All patients with a) adenoma or b) colorectal cancer
I: Number of specimen per year per capita and per institution, size and kind of institution (academic, community)
C: Not applicable
O: Optimal prognosis / mortality
S: (Systematic reviews of) diagnostic accuracy; inter-and intraobserver studies; biopsy diagnosis vs. specimen diagnosis

SEARCH METHOD

We searched MedLine databases from 1998 using the following search strategies:

First strategy
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* OR "Adenomatous Polyps"[Mesh])
AND (specimen* AND number* OR specimen* AND adequacy OR specimen* AND length)

Second strategy
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* OR "Adenomatous Polyps"[Mesh])
AND "Specimen Handling"[Mesh] AND ((Reproducibility of results[MH] OR stability OR storage OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation[MH] OR quality assurance OR quality control) OR (specificity OR sensitivity OR detection rate OR positive predictive value* OR negative predictive value* OR positive likelihood ratio* OR negative likelihood ratio* OR diagnostic Odds ratio OR ROC curve* OR false positive* OR false negative*)) AND ("Biopsy"[Mesh] OR biopsy OR "per year"[ti/ab] OR capita [ti/ab] OR academic [ti/ab] OR community [ti/ab])

We also searched the Cochrane Library.

RESULTS

We only found indirect data addressing this issue reported in five publications. A cross-sectional survey within a population based study evaluated the potential variation in reporting by laboratory type or hospital case volume. (1) High-volume hospitals were significantly more likely than low-volume hospitals to report how the specimen was received (p=0.007) and identified (p<0.001), and tumour site (p<0.05), macroscopic depth of penetration (p=0.002), and involvement of margins (p<0.001). Community hospital pathology laboratories were significantly less likely to report on how the specimen was identified (p<0.001) and on the macroscopic depth of penetration (p=0.03) than teaching hospital laboratories. Contract pathology laboratories were less likely to report the proximity to nearest margin (p=0.01), the macroscopic tumour subtype (p<0.05), and the macroscopic depth of penetration (p<0.001) compared with teaching hospital laboratories.

A population-based study involving stage II (T3N0 and T4N0) CRC cases retrieved using CRC pathology reports (1997–2000) from the Ontario Cancer Registry was aimed at analysing factors which affect lymph nodes assessment (2). Demographic, surgical, pathologic, and hospital data of 1789 patients aged 19 to 75 years were extracted and the results showed that significant factors associated with improved lymph node retrieval included young age, increased tumour size, increased specimen length, use of a pathology template and having surgery performed at an academic centre.

To investigate the variability in the accuracy of pathology reports, with special attention to differences between pathology departments and to their compliance to regional guidelines, a retrospective cohort study was performed, analysing data reported in the population-based register run by the Regional Oncologic Centre (ROC) in Sweden (3). Cumulative 5-year survival and differences in quality between pathology departments and their influence on the classification of tumours were evaluated in 3735 patients who had undergone resection of a colon cancer. The quality of the examination of a stage II or III colon cancer specimen, as measured by the number of lymph nodes examined, has an impact on the tumour staging and thus the management of the patient. In particular, survival rate was lower among stage II patients in whom fewer than 12 mesenteric lymph nodes (as stated in the recommendations) were examined than among those with 12 or more nodes examined (p=0.001, log-rank; 40 months follow-up in survivors). Overall there was a variation in the relative proportions of tumour stages II and III between different pathology departments, with less stage II, the more lymph nodes examined. These differences were not related to specific hospitals within the catchment area of the pathology department or to hospital category, but to the pathology departments themselves.

In two European cross-sectional studies biopsy was shown to be less accurate in establishing a definitive diagnosis than when the entire polyp is examined (4,5). In particular, biopsy-based diagnosis underestimated histopathological diagnosis in about 10% of colorectal adenomas detected by flexible sigmoidoscopy screening, while advanced neoplasia was underestimated in more than 60% (5).

CONCLUSIONS

No reliable data were found to assess whether the number of specimens per year, per capita and per institution and the size and kind of institution (academic, community) affects optimal prognosis/mortality of colorectal adenoma and cancer patients (LEVEL OF EVIDENCE V).

Biopsy appears less accurate in establishing a definitive diagnosis than when the entire polyp is examined (LEVEL OF EVIDENCE V).

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7.7.2   Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Wei 2004	Cross-sectional study within a population based study	To describe the completeness of pathology reporting for colon carcinoma, to evaluate potential variation in reporting by laboratory type or hospital case volume, and to identify areas for reporting improvement	438 pathology reports from T2-T4 surgically resected colon carcinoma patients USA	Recommendations of the Association of Directors of Anatomic and Surgical Pathology (ADASP)	Compliance with ADASP recommendations (presence or absence of recommended items)	<u>Hospital volume</u> High: 222 Medium: 126 Low: 31 High-volume hospitals were significantly more likely than low-volume hospitals to report how the specimen was received (p=0.007), was identified (p<0.001), tumour site (p<0.05), macroscopic depth of penetration (p=0.002), and involvement of margins (p<0.001). <u>Hospital type</u> Teaching: 115 Contract: 59 Community: 264 Community hospital pathology laboratories were significantly less likely to report on how the specimen was identified (p<0.001) and on the macroscopic depth of penetration (p=0.03) than teaching hospital laboratories. Contract pathology laboratories were less likely to report the proximity to nearest margin (p=0.01), the macroscopic tumour subtype (p<0.05), and the macroscopic depth of penetration (p<0.001) compared with teaching hospital laboratories.	**V** Pathology reports were effective in communicating most pertinent findings regarding surgically resected colon carcinoma. Variability in reporting based on laboratory affiliation and hospital case volume was observed.

Quality assessment: retrospective data collection; adequate representativeness of the population; no information on the blinded review of the reports.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Wright 2003	Cross-sectional study	To assess the adequacy of lymph node assessment in stage II CRC	1,789 T3N0M0 and T4N0M0 CRC patients aged 19 to 75 years Canada	Retrospective collection of data from the Ontario Familial Colorectal Cancer Registry and pathology reports from the Ontario Cancer Registry	*Number of lymph node assessed according to*: • patient age, • patient sex, • type of colorectal resection, • specimen length, • tumour size, • tumour stage; • type of hospital where colorectal resection was performed • use of pathology template for reporting	***Number of eligible case in which a lymph node assessment was done:*** 94/1789 (5.3%) ***Median lymph node assessed to render a diagnosis of node negative CRC:*** 8 (0-65) ***Relative average number of lymph node assessed per patient according to:*** Age 0.88 (95% CI 0.84-0.93); p=0.0004 Sex (male vs. female) 1.02 (95% CI 0.93–1.11); p=0.73 Tumour size 1.97 (95% CI 1.7–2.27); p<0.0001 Stage (T3 vs. T4) 1.02 (95% CI 0.9–1.16); p=0.78 Specimen length 1.06 (95% CI 1.04–1.09); p=0.004 Cases per hospital 1.24 (95% CI 0.75–2.03); p=0.42 Template use 1.27 (95% CI 1.13–1.43); p=0.0004 Academic centre versus non-academic centre 1.47 (95% CI 1.27–1.7); p=0.0004 ***Patients characteristics in academic vs. non-academic hospital*** no difference in age, sex, tumour size, or tumour stage between these two groups. There was a trend toward a shorter specimen length in cases from non-academic hospitals (p=0.076).	**V** Significant factors associated with improved lymph node retrieval included young age, increased tumour size, increased specimen length, use of a pathology template, and having surgery performed at an academic centre.

Quality assessment: retrospective data collection; adequate representativeness of the population; no information on the blinded review of the reports.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Jestin 2005	Retrospective cohort study	To investigate the variability in the accuracy of pathology reports, with special attention to differences between pathology departments and to their compliance to regional guidelines	3,735 patients who had undergone resection of a colon cancer. Gender ratio (M:F) 1,817/1,918 Mean age (ranges); year Male: 71 (19–98) Female: 73 (12–98) Sweden	Analysis of data reported in the population-based register run by the Regional Oncologic Centre (ROC)	Cumulative 5-year survival Differences in quality between pathology departments and their influence on the classification of tumours into stages	**Stage I tumours (N=434)** No significant differences on survival rate according to the number of examined lymph node **Stage II tumours (N=1554)** Number of lymph nodes examined reported: 1049/1554 (68%) Survival rate was lower among patients in whom fewer than 12 mesenteric lymph nodes (as stated in the recommendations) were examined than among those with 12 or more nodes examined (p=0.001; follow-up in survivors 40 months) **Stage III tumours (N=1151)** Survival rate was lower among patients N2-tumours (P <0.001) **Number of resections, cases where number of lymph nodes examined is given (%) and number of lymph nodes examined according to pathology department (range):** A: 593; 323 (54); 6 (0–30); B: 621; 339 (55); 6 (0–57); C: 550; 403 (73); 9 (1–38); D: 496; 277 (56); 6 (0–23); E: 528; 431 (82); 9 (0–43); F: 487; 346 (71); 12 (1–49); G: 460; 271 (59); 11 (0–39); All: 3735; 2390 (64); 8 (0–57). Three of the departments (A, B, D) examined significantly fewer nodes compared to the other four departments (median 6 compared to ≥9; p<0.001)	**III** The quality of the examination of a stage II or III colon cancer specimen, as measured by the number of lymph nodes examined, has an impact on the tumour staging and thus the management of the patient. Overall there was a variation in the relative proportions of tumour stages II and III between different pathology departments, with less stage II the more lymph nodes examined. These differences were not related to specific hospitals within the catchment area of the pathology department or to hospital category, but to the pathology departments themselves.

*TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma, HP, hyperplastic polyp.

Quality assessment: retrospective data collection; adequate cancer population representativeness; clear definition of the intervention and adequate ascertainment of exposure; adjustment factors not reported; no information of blinded assessment of outcomes.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Absar 2004	Cross-sectional study	To assess the incidence of change in histopathological diagnosis of polyps when comparing biopsy with snared specimen	566 patients who had colonic polyps detected during endoscopy. UK	All polyps biopsied were snared and retrieved and sent for histopathological examination	Number of biopsies initially showing adenomatous changes only but on excision (endoscopic or surgical) were proven to be adenocarcinoma	*Histological diagnosis of polyps (%):* Malignant 27 (3.2%) Tubular adenoma 262 (30.9%) Tubulovillous adenoma 61 (7.2%) Villous adenoma 85 (10.0%) Hyperplastic polyp 292 (34.4%) Inflammatory 46 (5.4%) Normal mucosa 76 (8.9%) *Diagnosed based on total polyp specimen (N=282) according to type of polyp:* Malignant: 27 Tubular adenoma: 159 Tubulovillous adenoma: 34 Villous adenoma: 62 *Number of polyps in which diagnosis changed according to type of polyp** Malignant: 5 (TA-4, TVA-1) Tubular adenoma: 11 (TVA-6, VA-4, HP-1) Tubulovillous adenoma: 8 (TA-4, VA-3, HP-1) Villous adenoma: 11 (TA-7, TVA-4) *Percentage change in diagnosis according to type of polyp:* Malignant: 1.8 (5/282) Tubular adenoma: 3.9 (11/282) Tubulovillous adenoma: 2.8 (8/282) Villous adenoma: 3.9 (11/282)	**V** After snaring there was a change in diagnosis in 35 out of 282 polyps. Two previously reported hyperplastic polyps which were found to be neoplastic. Biopsy showed adenomatous features only in five malignant polyps. 11 cases of tubular adenomas, 8 cases of tubulovillous adenoma and 11 cases of villous adenoma, changed label into another adenomatous variant. Biopsy appears less accurate in establishing a definitive diagnosis than when the entire polyp is examined.

*TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma, HP, hyperplastic polyp.

Quality assessment: N/A

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Gondal 2005	Cross-sectional study	To assess the validity of a cold biopsy specimen as representative for the whole polypectomy specimen, with regard to histopathological features	442 who fulfilled the criterion of colonoscopic recovery of adenoma that had been biopsied at flexible sigmoidoscopy. 60% men Norway	Polypectomy (snare resection) of adenoma previously diagnosed by biopsy	Change in histopathologic diagnosis of adenoma comparing biopsy and polypectomy	Assessment of intraepithelial neoplasia (dysplasia) status was changed in 51 adenomas (10%). 38 cases (7%) were underestimated by biopsy compared with polypectomy. Assessment of villousness was changed in 45 adenomas (9%), being upgraded in 26 (6%) at polypectomy. Diameter of neoplasia was positively associated with increased risk of the underestimation of intraepithelial neoplasia and/or villousness (ptrend=0.01).	**V** Biopsy-based diagnosis underestimated histopathological diagnosis in about 10% of colorectal adenomas detected by flexible sigmoidoscopy screening. Advanced neoplasia was underestimated in more than 60%.

*TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma, HP, hyperplastic polyp.

Quality assessment: data were extracted from the abstract as we were unable to retrieve the article full text.

7.8 Impact of proforma reporting on the quality of a screening programme or reporting of colorectal cancer

7.8.1 Summary document

Rita Banzi

CLINICAL QUESTION 9

Is there evidence that proforma reporting improves the quality of a screening programme, or reporting of colorectal cancer?

PICOS

P: All patients with colorectal cancer
I: Standardised proforma reporting
C: Non standardised reporting
O: Optimal quality measured by prognosis / mortality
S: (Systematic reviews of) diagnostic accuracy; cross-sectional studies, case series

SEARCH METHOD

We searched MedLine and Embase databases using the following search strategies:
("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* OR "Adenomatous Polyps"[Mesh]) AND reporting AND (standard* OR proforma) OR "Medical Records/standards"[Mesh]

We also searched the Cochrane Library and we retrieved additional studies from the analysis of literature quoted in the considered papers.

RESULTS

One RCT (1), 4 cohort studies (3-6) and 3 cross-sectional studies were considered for these issues (8-10). An RCT with a split unit design and stratified cluster randomisation involved 16 hospital pathology laboratories in Wales which were randomly allocated to report either breast or colorectal resection specimens by computerised form or conventional free text (1). The use of pre-defined forms similar to those issued by the Royal College of Pathologists (2) led to a 28.4% (95% CI 15.7%–41.2%) increase in complete reporting of a minimum dataset required for cancer registration and a 24.5% (95% CI 11.0%–38.0%) increase in complete reporting of minimum data required for patient management.

Two UK cohort studies assessed the quality and completeness of reporting after the introduction of the Royal College of Surgeons/Association of Coloproctology proforma (3,4). A relevant decrease in

the number of missing items was observed (from 85% to 18% after the introduction of the proforma, p <0.001), with a statistically significant increase in reporting of circumferential resection margins, apical node status, and vascular invasion. Moreover, a British cohort study within a regional audit investigated the effect of the introduction of guidelines published in book format and in a flow chart format, and the introduction of an initial proforma (developed within the audited department) and a second proforma (Royal College of Surgeons/Association of Coloproctology-RCS/ACP national guidelines minimum dataset) (5). All interventions produced some increase in inclusion rate for some features, but only with the introduction of template proforma did these rates approach 100% for all data items. Inclusion rates were 100% for all items in all cases reported using a proforma. In the final audit period the 96% of specimens were reported using proforma. A retrospective comparative study conducted in the UK confirmed this trend, reporting a statistically significant increase in the reporting of background pathological abnormality (i.e diverticular disease, synchronous adenomas, ulcerative colitis), histological differentiation, extramural vascular invasion, Dukes' stage, TNM stage, apical node, median number of nodes (IQR) after the introduction of a standardised pathology proforma (6).

An improvement of the quality and completeness of histopathology reports of colorectal cancer was reported in several cross-sectional and population based audit studies (8-10). An American study in which the authors reviewed pathology reports for compliance with recommendations of the Association of Directors of Anatomic and Surgical Pathology (ADASP) (7) showed limited compliance for descriptions of how specimen was received (68%), how specimen was identified (71%), macroscopic depth of penetration (82%), appearance of serosa adjacent to tumour (50%), and status of residual bowel (73%) (8). All other criteria were reported in more than 90% of patients. Lastly, two European cross-sectional studies confirmed that the quality and completeness of histopathology reports of colorectal cancer is low and despite its documented value as an important predictor of local recurrence, circumferential margin involvement is too frequently omitted (9,10).

CONCLUSIONS

High-quality reporting of colorectal cancer appears to be very important both to the clinicians treating the patients and to the Cancer Registry. For these reasons the introduction of a 'minimum' data proforma template allows a more complete reporting compared with interpretation of free text reports by medical staff (LEVEL OF EVIDENCE II, III).

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7.8.2 Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Branston 2002	RCT	To determine whether reporting guidelines and computerised form-based reports improve the completeness of histopathological cancer data available for patient management and population cancer registration and to evaluate the acceptability of the intervention	16 hospitals; 2042 reports Wales	*Overall* Pre-defined form arm (CROPS reporting screen): 1044 reports Control arm: 998 *Breast cancer* Pre-defined form arm (CROPS reporting screen): 602 reports Control arm: 539 *CRC cancer* Pre-defined form arm (CROPS reporting screen): 442 reports Control arm: 459	Completeness of data available to clinicians	680 specimens had not received a form report in the study arm <u>Whole form</u> ***increase in complete reporting of a minimum dataset required for cancer registration*** 39.4% (95% CI 27.6–51.3%) ***increase in complete reporting of minimum data required for patient management*** 29.3% (95% CI: 15.0–43.7%) <u>Essential cancer registry items</u> ***increase in complete reporting of a minimum dataset required for cancer registration*** 28.4% (95% CI 15.7–41.2%) ***increase in complete reporting of minimum data required for patient management*** 24.5% (95% CI: 11.0–38.0%) Form-based reporting was acceptable to pathologists and preferred by clinicians.	**II** a package of guidelines and computerised forms made a significant impact on the completeness of data available, both to the clinicians treating the patients and to the Cancer Registry, compared with interpretation of free text reports by medical staff and Cancer Registry coders

Quality assessment: cluster randomisation with hospital allocation; 2x2 split unit analysis; stratification according to workload, screening programme, type of computer system used; each pathologist attended a training programme on test cancer site and on the use of the computer forms. No information on generation and allocation of the randomisation sequence. No power calculation. Blindness not performed.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Rigby 1999	Cohort study	To assess how the use of a proforma affected the completeness of reporting within one hospital	54 colorectal cancer patients attending one teaching hospital UK (Sheffield)	Royal College of Surgeons/Association of Coloproctology proforma	Quality and completeness of reporting	***One or more items missing from their report*** before introduction of the proforma: 46/54 (85%) after introduction of the proforma: 8/44 (18%) p <0.001 ***Circumferential resection margins and apical node status*** more frequently reported after the proforma introduction p <0.05 and p <0.001 ***Median number of lymph nodes harvested*** No difference after proforma introduction	**III** The introduction of the proforma resulted in improvements in reporting histopathology features of colorectal cancer patients

Quality assessment: Prospective design; adequate cancer population representativeness; pathologists are selected from a teaching hospital; clear definition of the intervention (proforma introduction) and adequate ascertainment of exposure; adjustment factors not reported; no information of blinded assessment of outcomes.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Oppong 2002	Cohort study	To assess how the use of a proforma affected the completeness of reporting within one hospital	20 rectal cancer pathology reports from 1998 20 reports from the years preceding the introduction of the proforma (1995). 50 colon cancer and 50 rectal cancer reports from 1999 UK (Plymouth)	Royal College of Surgeons/Association of Coloproctology proforma	Quality and completeness of reporting	***Circumferential resection margins (rectal cancer)*** 1995: 30% 1998: 95% 1999: 96% (p <0.001) ***Apical node status*** 1995: 8% 1998: 85% 1999: 96% (p <0.001) ***Vascular invasion*** 1995: 50% 1998: 85% 1999: 96% (p <0.001)	**III** A highly significant improvement in the quality of reporting was noted and maintained

Quality assessment: Not performed as data were extracted from a letter. We were unable to find other publications which report these results.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Cross 1998	Cohort study	To investigate the effect of different interventions on the inclusion of data items in the histopathology reports of resected colorectal cancer	272 histopathology reports UK (Sheffield)	Five consecutive audit point: 1: April 1993 free text reporting with no agreed content of reports 2: November 1993 agreed guidelines published in book format 3: July 1996 agreed guidelines published in a flow chart format 4: January 1997 initial proforma (developed within the audited department) 5:November 1997 second proforma (Royal College of Surgeons/Association of Coloproctology-RCS/ACP national guidelines minimum dataset)	Quality and completeness of histopathology reports	*No of reports* April 1993: 50 November 1993: 50 July 1996: 43 January 1997: 61 November 1997: 68 *Type* April 1993: 100% November 1993: 100% July 1996: 100% January 1997: 100% November 1997: 100% *Grade* April 1993: 98% November 1993: 98% July 1996: 100% January 1997: 100% November 1997: 100% *Depth of invasion* April 1993: n/a November 1993: n/a July 1996: 100% January 1997: 100% November 1997: 100% *Vascular invasion* April 1993: n/a November 1993: n/a July 1996: 88% January 1997: 97% November 1997: 100% *Circumferential resection margin* April 1993: 31% November 1993: 68% July 1996: 86% January 1997: 97% November 1997: 100%	**III** All interventions produced some increase in inclusion rate for some features, but only with the introduction of template proformas did these rates approach 100% for all data items. Inclusion rates were 100% for all items in all cases reported using a proforma. In the final audit period 96% of specimens were reported using proformas.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Other resection margins April 1993: n/a November 1993: n/a July 1996: 54% January 1997: 97% November 1997: 100% ***Lymph node status*** April 1993: 98% November 1993: 98% July 1996: 100% January 1997: 100% November 1997: 100% ***Background mucosa*** April 1993: n/a November 1993: n/a July 1996: 65% January 1997: 97% November 1997: 99% ***Dukes' stage*** April 1993: 72% November 1993: 86% July 1996: 100% January 1997: 97% November 1997: 100% ***TNM stage*** April 1993: n/a November 1993: n/a July 1996: 0% January 1997: 2% November 1997: 97% ***Use of proforma*** April 1993: 0% November 1993: 0% July 1996: 0% January 1997: 84% November 1997: 96%	

Quality assessment: It is not clear whether a retrospective or prospective data collection was performed.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Beattie 2003	Retrospective comparative study-retrospective cohort	To assess if the introduction of a comprehensive standardized pathology proforma improved the quality and completeness of histopathology reporting in CRC resection specimens	1996 pathology reports: 85 2000 pathology reports: 86 UK	Introduction of a comprehensive standardized pathology proforma in 1998	Quality and completeness of histopathology reporting in CRC resection specimens	***Demographic details*** 1996: 85 (100%); 2000: 86 (100%); Not significant ***Incomplete clinical data*** 1996: 57 (67%); 2000: 63 (73%); Not significant ***Distance of tumour from distal resection margin*** 1996: 80 (94%); 2000: 86 (100%); Not significant ***Background pathological abnormality (i.e diverticular disease, synchronous adenomas, ulcerative colitis)*** 1996: 18 (21%); 2000: 80 (93%); $p<0.001$ ***Histological differentiation*** 1996: 73 (86%); 2000: 86 (100%); $p<0.01$ ***Extramural vascular invasion*** 1996: 58 (68%); 2000: 86 (100%); $p<0.001$ ***Dukes' stage*** 1996: 33 (39%) but calculable in 84 (99%) of the 85 reports; 2000: 86 (100%); $p<0.01$ ***TNM stage*** 1996: 0 (0%); 2000: 84 (98%); $p<0.001$	**III** The introduction of a standardized proforma for reporting CRC resection specimens improves the quality of histopathological reporting.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Apical node (involved or not involved) 1996: 34 (40%); 2000: 85 (99%); p<0.01 ***Median number of nodes (IQR)*** 1996: 9 (5–12); 2000: 12 (8–17); p<0.01 ***Adequacy of resection*** 1996: 74 (87%); 2000: 86 (100%); p<0.01 ***Number of rectal specimen reports*** 1996: 24 (28%); 2000: 40 (47%); ***Circumferential resection margin*** 19/24 (79%); 38/40 (95%); Not significant ***Relationship to peritoneal reflection*** 1 (1%); 30 (75%); p<0.01	

Quality assessment: retrospective design; data were identified from colorectal department records and cross-referenced with pathology department records.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Wei 2004	Cross-sectional study within a population based study	To describe the completeness of pathology reporting for colon carcinoma, to evaluate potential variation in reporting by laboratory type or hospital case volume, and to identify areas for reporting improvement	438 pathology reports from T2-T4 surgically resected colon carcinoma patients USA	Recommendations of the Association of Directors of Anatomic and Surgical Pathology (ADASP)	Compliance with ADASP recommendations (presence or absence of recommended items)	Macroscopic description *How specimen was received* 68.4% *How specimen was identified* 71.5% *Parts included* 100% *Tumour site* 99.3% *Proximity to nearest margin* 93.6% *Macroscopic subtype* 99.3% *Tumour dimensions* 94.1% *Macroscopic depth of penetration* 81.7% *Appearance of serosa adjacent to tumour* 49.5% *Status of residual bowel* 73.3% Histologic information *Histologic type* 100% *Histologic grade* 97.9% *Depth of infiltration* 97.9% *Lymph node metastases* 99.3% *Involvement of margins* 93.8% Hospital volume High: 222 Medium: 126 Low: 31 High-volume hospitals were significantly more likely than low-volume hospitals to report how the specimen was received (p=0.007), was identified (p<0.001), tumour site (p<0.05), macroscopic depth of penetration (p=0.002), and involvement of margins (p<0.001). Hospital type Teaching: 115 Contract: 59 Community: 264	**V** Pathology reports were effective in communicating most pertinent findings regarding surgically resected colon carcinoma. Variability in reporting based on laboratory affiliation and hospital case volume was observed.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Community hospital pathology laboratories were significantly less likely to report on how the specimen was identified (p<0.001) and on the macroscopic depth of penetration (p=0.03) than teaching hospital laboratories. Contract pathology laboratories were less likely to report the proximity to nearest margin (p=0.01), the macroscopic tumour subtype (p<0.05), and the macroscopic depth of penetration (p<0.001) compared with teaching hospital laboratories.	

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Bull 1997	Population based audit	To audit the information content of pathology reports of colorectal cancer specimens in one National Health Service region.	1,242 histopathology reports UK (Wales)	Recording on a proforma by a single surgical research fellow of pathology reports	Completeness of histopathology reports	<u>All tumours:</u> **Length of specimen** 98.4 **Tumour size** 94.4 **Distance from resection end** 75.2 **Appearance of tumour** 92.0 **Histological type** 100.0 **Histological grade** 100.0 **Extent of invasion** 98.6 **Resection end involvement** 92.3 **Whether nodes involved** 95.3 **Number of nodes involved** 27.5 **Dukes' stage** 73.6 <u>For rectal tumours only:</u> **Circumferential plane involvement** 57.6 **Measured circumferential plane clearance** 7.7	**V** The informational content of many routine pathology reports on colorectal cancer resection specimens is inadequate for quality patient management, for ensuring a clinically effective cancer service through audit, and for cancer registration. Template proforma reporting using nationally agreed standards is recommended.

Quality assessment: N/A.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Eon 2006	Cross-sectional study	To audit quality and completeness of histopathology reports of rectal cancer resections in Brittany by comparing results with French guidelines	16 pathology laboratories; 234 patients, 58% males; mean age 66.5±10.4 years Brittany, France patients were included when the insurance fund received a request for 100% coverage for a special examination protocol	N/A	Quality and completeness of histopathology reports	Administrative data *Registration number* 233/234 (99.5%) *Freezing number for special techniques* 0 (0%) Clinical data *Type of surgical resection* 87/234 (37%) Operative specimen *Preparation* 60/234 (26%) *Tumour localisation* 233/234 (99.5%) *Length of resection specimen* 229/234 (98%) Gross aspect of tumour *Height* 220/230 (96%) *Width* 96/230 (42%) *Thickness* 75/230 (31%) *At least one dimension* 220/230 (96%) *Circumferential extension* 141/230 (61%) *Margin measurements* 182/230 (79%) *Tumour aspect* 198/230 (86%) *Presence or absence of perforation mentioned* 25/230 (11%) *Presence or absence of polyps mentioned* 59/230 (25%) *Presence or absence of metastases mentioned* 62/230 (26%) Tumour histology *Adenocarcinoma differentiation* 174/225 (77%) *Presence or absence of colloid component mentioned* 51/230 (23%) *% with colloid component* 39/51 (76%) Deep invasion 225/230 (98%) Surgical resection *Longitudinal margins* 215/234 (92%) *Circumferential margins* 62/234 (27%)	V The quality and completeness of histopathology reports of rectal cancer resections in Brittany appears low. In particular, despite its documented value as an important predictor of local recurrence, circumferential margin involvement is too frequently omitted.

Author, publication year	Study design	Objective	Participants	Intervention	Outcome	Results	Level of evidence Conclusions
						Extension **Number of nodes examined** 204/234 (87%) **Number of positive nodes** 217/234 (93%) **Presence or absence of vascular invasion mentioned** 79/234 (34%) **Presence or absence of perineural invasion mentioned** 42/234 (18%) Conclusion **Staging by UICC Classification** (pTNM) 143/234 (67%) **Tumour residue mentioned** 15/234 (7%)	

7.9 Impact of advanced polyp measurement on diagnostic reproducibility and advanced adenoma detection rate

7.9.1 Summary document

Rita Banzi

CLINICAL QUESTION 10

Do different modalities of advanced polyp measurement (endoscopic measurement vs. pathologist's measurement - before and after fixation, slide preparation) affect diagnostic reproducibility and the detection rate of advanced adenomas in a screening setting?

PICOS

P: Symptomatic and asymptomatic people detected with polyps
I: Endoscopic polyp measurement, measurement before fixation, slide preparation
C: Pathologist's measurement; measurement after fixation; different modalities of slide preparation
O: Diagnostic reproducibility and detection rate of advanced adenomas: (Systematic reviews of) diagnostic accuracy studies, observational studies; cross-sectional studies, case series

SEARCH METHOD

We searched MedLine (1966-2008) using the following search strategy:
(("Colonic Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp* OR "Adenomatous Polyps"[Mesh]) AND
("endoscopist*" OR "pathologist*") AND (Reproducibility of results [MH] OR reliability OR reproducibility OR agreement OR kappa OR Observer Variation[MH])]

We also extensively hand-searched references quoted by the included studies and reported as PubMed related links.

RESULTS

We included evidence from three studies (1-3) all performed in the USA during the last 90s. A comparison of the size of polyps estimated in vivo at the time of colonoscopy (endoscopic measurement of the polyps made using biopsy forceps as a guide) versus ex vivo after removal, both before and after fixation was conducted on 31 pedunculated polyps in 25 patients (1). The authors reported that endoscopists overestimated the size of 74% of a sample of 31 polyps. The mean difference between estimate of polyp size and mean postpolypectomy measurement (assessed by a blinded technician) was significantly larger on average than postpolypectomy measurements (1.6 mm, 18%, p <0.05).

Schoen et al. compared the estimates of ten endoscopists and an independent pathologist measurements and the effect of formalin fixation on polyp size and interobserver variability (2). Interobserver agreement between pathologists' and the investigator's post-formalin measurements showed that 55 of 57 polyps (97%) were within ±0.3 cm. Endoscopists inaccurately estimated 11 of 56 polyps (20%) (>0.3 cm difference from the independent examiner). Polyp size was underestimated in three instances (range 0.5 to 0.9 cm) and overestimated in eight (range 0.4 to 0.8 cm). In 5 of 11 instances (46%), this inaccuracy altered polyp size classification across the 1 cm threshold.

When five methods of estimating polyp size during colonoscopy (visual estimation, open biopsy forceps, linear probe, ruler immediately after excision-gold standard, and ruler after fixation in formalin) were compared on 100 polyps, the difference in measurement between the actual size and the visual, probe, and forceps methods was 23% to 27.9% for polyps 5 mm or less, 0.4% to 14.4% for polyps between 5.01 mm and 10 mm, and 0.4% to 6.8% for polyps larger than 1 cm. The size of all of the polyps after fixation was 12% to 18% smaller than the actual size measured soon after retrieval. For all (100) polyps the mean difference versus the actual size of polyps was 3.4% for linear probe, 6.4% for visual estimation, and 12.3% for the forceps. (3)

CONCLUSION

Although the quality of evidence is low, there is some indication that different modalities of advanced polyp measurement (endoscopic measurement vs. pathologist's measurement-before and after fixation, slide preparation) can affect diagnostic reproducibility and the detection rate of advanced adenomas. An overestimation or underestimation of a large or a small polyp is more likely to be important when the misjudgement crosses the 1 cm threshold. It seems that the use of the pathologist's measurement would be more accurate (LEVEL OF EVIDENCE V).

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7.9.2 Evidence tables

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Gopalswamy 1997	Five methods of estimating polyp size during colonoscopy: 1. visual estimation, 2. open biopsy forceps 3. linear probe, 4. ruler immediately after excision, Gold standard 5. ruler after fixation in formalin	Cross-sectional study	100 polyps (50 tubular adenomas, 26 tubulovillous adenomas, 4 villous adenomas, 16 hyperplastic polyps, and 4 non-neoplastic polyps) USA	Accuracy of different estimating polyp size techniques	***All Polyps*** <u>Number of polyps</u> 100 for all five methods <u>Mean size</u> Actual size 7.07 Visual estimation 7.52 Open biopsy forces 7.94 Linear probe 7.31 Histologic size 5.99 <u>Mean difference vs. actual size (95% CI)</u> Visual estimation 0.45 (0.08,0.82); p≤0.05 Open biopsy forces 0.87 (0.43, 1.31); p≤0.001 Linear probe 0.24 (-0.16, 0.64); Histologic size -1.08 (-1.54,-0.62); p≤0.001 <u>% difference vs. actual size</u> Visual estimation 6.4 Open biopsy forces 12.3 Linear probe 3.4 Histologic size 15.3 <u>Pearson correlation with actual size</u> Visual estimation 0.90 p≤0.001 Open biopsy forces 0.88 p≤0.001 Linear probe 0.88 p≤0.001 Histologic size 0.85 p≤0.001 ***Polyps from 5.01 mm to 10 mm*** <u>Number of polyps</u> 33 for all five methods <u>Mean size</u> Actual size 7.76 Visual estimation 7.73 Open biopsy forces 8.88 Linear probe 7.86 Histologic size 6.82 <u>Mean difference vs. actual size (95% CI)</u> Visual estimation -0.03 (-0.69,0.63); Open biopsy forces 1.12 (0.24, 2.00); p≤0.05 Linear probe 0.1 (-0.65, 0.85); Histologic size -0.94 (-1.88, 0.00); p≤0.05	**V** Measurement of polyp size by linear probe agreed best with the actual polyp size, followed closely by visual estimation. The open biopsy forceps method was the least accurate. Thus, the visual method of measuring polyps is sufficient for daily practice, but for research studies we recommend that the actual size of polyps be measured after retrieval or that a linear probe be used to measure polyp size at colonoscopy

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
					<u>% difference vs. actual size</u> Visual estimation 0.4 Open biopsy forces 14.4 Linear probe 1.3 Histologic size 12.1 <u>Pearson correlation with actual size</u> Visual estimation 0.57 p≤0.001 Open biopsy forces 0.60 p≤0.001 Linear probe 0.62 p≤0.01 Histologic size 0.22 p≤0.001 ***Polyps greater than 10 mm*** <u>Number of polyps</u> 20 for all five methods <u>Mean size</u> Actual size 13.95 Visual estimation 14 Open biopsy forces 14.05 Linear probe 13 Histologic size 11.45 <u>Mean difference vs. actual size (95% CI)</u> Visual estimation 0.05 (-12.0, 1.30); Open biopsy forces 0.1 (-1.36, 1.56); Linear probe -0.95 (-2.28, 0.38); Histologic size -2.5 (-4.03, 0.97); p≤0.01 <u>% difference vs. actual size</u> Visual estimation 0.4 Open biopsy forces 0.7 Linear probe 6.8 Histologic size 17.9 <u>Pearson correlation with actual size</u> Visual estimation 0.65 p≤0.01 Open biopsy forces 0.70 p≤0.001 Linear probe 0.58 p≤0.01 Histologic size 0.63 p≤0.01	

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Morales 1996	Comparison of the size of polyps estimated in vivo at the time of colonoscopy (endoscopic measurement of the polyps made using biopsy forceps as a guide) versus ex vivo after removal, both before and after fixation	Cross-sectional study	31 pedunculated polyps in 25 patients mean age: 64 years (range, 34 to 78) 21 men and 4 women USA	Mean difference between estimate of polyp size and mean postpolypectomy measurement (assessed by a blinded technicians)	<u>histologic diagnoses of the polyps</u> 13 tubular adenomas, 12 tubulovillous adenomas, 2 hyperplastic polyps, 1 villous adenoma, 1 juvenile polyp, 1 hamartomatous polyp. <u>estimate of polyp size</u> 8.9 mm <u>mean postpolypectomy measurement</u> 7.3 mm <u>mean difference</u> 1.6 mm, 18% (p <0.05) (90% CI 1.0 to 2.1 mm) 23/31 (74%) of the endoscopic estimates of polyp size were larger than the postpolypectomy measurement <u>mean difference for polyps 1 cm or larger</u> 2.4 mm <u>mean difference for polyps 1 cm or smaller</u> 1.4 mm <u>mean post-polypectomy measurements</u> 7.3 mm <u>post-fixation measurements</u> 7.1 mm No statistically significant	**V** The size of polyps measured endoscopically is significantly larger on average than postpolypectomy measurements. These data emphasize the need for systematic and uniform measurement of polyps, particularly in the setting of clinical studies

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schoen 1997	Comparison between endoscopists' estimates and pathologists' measurements (made by an independent examiner) The effect of formalin fixation on polyp size and the interobserver variability in measurement were also evaluated	Cross-sectional study	Ten endoscopists removed 61 polyps with a snare in 33 patients USA	Mean difference between endoscopists' estimates and pathologists' measurements (assessed by a blinded technicians) Interobserver variability Agreement in polyp size estimation	<u>Polyp mean size</u> 0.85±0.6 (SD) range: 0.3 to 3.6 cm, 26% ≥1 cm Polyps neither consistently shrank nor enlarged in formalin (maximal change ±0.2 cm, r = 0.99, p <0.001) <u>Number of polyps measured the same or within 1 mm</u> of each other between pathologists' and the investigator's post-formalin measurements 46/57 (81%) <u>Number of polyps measured within ± 0.3 cm</u> of each other between pathologists' and the investigator's post-formalin measurements 55/57 (97%) <u>Number of polyps with a 0.4 cm difference</u> 2/57 (3%) r = 0.98, p <0.001 <u>Mean size difference</u> (excluding the five polyps which fragmented between the endoscopist's estimate and the investigator's measurement before formalin fixation) 0.08 ± 0.3 cm (range:-0.9 to 1.0 cm) <u>Endoscopists inaccurate estimation</u> 11/56 polyps (20%) (>0.3 cm difference from the independent examiner). <u>Endoscopist underestimation</u> 32.1% same estimation 12.5%, <u>Endoscopist overestimation</u> 55.4%	**V** Polyp size is not significantly affected by formalin fixation. Endoscopists' estimates of polyp size are often unreliable: in 5 of 11 instances the endoscopist's inaccurate estimation of polyp size could have affected patient management. Use of the pathologist's measurement would have been accurate in every instance. When possible pathologists' measurements of polyp size should be used in clinical trials and in clinical practice.

7.10 Sessile serrated polyps, serrated adenomas, and hyperplastic polyps management

7.10.1 Summary document

Rita Banzi

CLINICAL QUESTION 11

What is the currently available evidence on sessile serrated polyps, serrated adenomas, and hyperplastic polyp management?

PICOS

P: Symptomatic and asymptomatic people detected with sessile serrated polyps, serrated adenomas, and hyperplastic polyps
I: Treatment and follow-up modalities
C: Not applicable
O: Optimal prognosis /mortality/CRC incidence: observational studies; cross-sectional studies, case series

SEARCH METHOD

We searched MedLine (1966-2008) using the following search strategy:
("SESSILE SERRATED ADENOMA" OR "SERRATED POLYP" OR "HYPERPLASTIC POLYP") AND
Colorectal Neoplasm [Mesh]

We also extensively hand-searched references quoted by the included studies and reported as PubMed related links and literature suggested by the authors.

RESULTS

We found no longitudinal studies assessing how different treatments or follow up of sessile serrated polyps, serrated adenomas, and hyperplastic polyps affect clinical outcomes of interest.

We included in this summary two narrative reviews (1,2) and four original studies (3-6) in order to report the available evidence on the history, nomenclature, classification, diagnosis, and management of serrated polyps.

Both reviews (1, 2) agree that hyperplastic polyps (HP) of the colorectum are heterogeneous lesions, a subset of which is now regarded as the precursor of colorectal cancer with DNA microsatellite instability. Some authors have distinguished this subset from classic HP and have introduced the term "sessile serrated adenoma" (SSA). Features of HP with increased malignant potential include large size, multiplicity, location in the proximal colon, and a sessile growth pattern. HP with malignant potential has been distinguished from classic HP on the basis of subtle microscopic features that

include increased serration, crypt dilatation, horizontal crypts, and hypermucinous epithelium. However, histological distinction between classic HP and SSA cannot be achieved in all cases. Although most right sided HP or SSA will not progress to cancer, the magnitude of risk is probably comparable to that of traditional colorectal adenoma. Clinicians should be made aware of the increased malignant potential of right sided HP or SSA.

A case series study published in 2008 (3) evaluated 185 serrated polyps extracted from the internal pathology database which was searched for polypectomy specimens removed between July 2003 and June 2005. This study reported that interobserver agreement for the diagnosis of serrated polyps was moderate. Concordance for HP and SSA was moderate (K=0.45508 and 0.51996 respectively) whereas it was nearly perfect for traditional serrated adenoma TSA (K=0.80954). Moreover, providing information on polyp site and size did not improve concordance. All observers relied more often on architectural features than on cytological ones to distinguish SSA from HP and agreement was reached that architectural features should provide the basis for the diagnosis of SSA. After this consensus interobserver concordance was slightly improved but remained moderate (k=0.58).

The other three original studies all deal with classification and clinicopathological feature description.

A study aimed at characterizing a series of colorectal polyps, focusing on the clinicopathological features of serrated adenoma (SA), mixed polyp (MP) and sessile serrated adenoma (SSA) was performed in Canada (4). 891 conventional adenomas (AD), 298 HP, 27 SSA, 10 (mixed polyp) MP and 24 traditional serrated adenoma (SA) obtained from patients during colonoscopic examination were analysed. The study found that frequency of SSA to be approximately 2% of all polyps removed colonoscopically. SSA accounted for 8.3% of polyps that would previously have been diagnosed as HP. Classical HP usually presents in the left colon and rectum. SSA was more likely to be right-sided than HP (p<0.0003). Torlakovic et al. found a higher proportion of SSA (18%) among lesions that would previously have been diagnosed as HP (5). However, this study also reported that SSA shows a predilection for the proximal colon.

The last included study (6) compared a study group which included 106 hyperplastic-like, non-adenomatous, serrated polyps, most from the ascending colon in 91 patients and a control group including 106 rectosigmoid hyperplastic polyps from 106 patients in whom adenocarcinoma did not develop. Study group polyps had an expanded crypt proliferative zone, a serrated architectural outline that became apparent in the basilar crypt regions, basilar crypt dilation, inverted crypts, and a predominance of dysmaturational crypts (crypts with minimal cell maturation). In contrast, control group polyps had polyps with a proliferative zone confined to the basal crypt region, serrated architecture that became apparent in the superficial crypt region, rare to no basilar crypt dilation, and rare or no dysmaturational crypts. These morphologic features provide initial guidelines to identify this potentially important subset of premalignant serrated-like polyps

CONCLUSIONS

Few data were retrieved on this issue. This lack of data caused in part by the confusion in terminology in most current literature and a lack of good prospective studies preclude a clear indication on the optimal treatment and follow up strategy for sessile serrated polyps, serrated adenomas and hyperplastic polyps (LEVEL OF EVIDENCE V).

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2. Higuchi T & Jass JR (2004), My approach to serrated polyps of the colorectum, *J.Clin.Pathol.*, vol. 57, no. 7, pp. 682-686.

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7.10.2 Evidence tables

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Farris 2008	Original classification vs. classification performed by five pathologists with a special interest in GI pathology blinded to clinical and demographic data (1st round) and then provided with the location and endoscopic size of each polyp (2nd round) A third round was performed after a consensus conference	Case series

The aim of our study was to determine whether serrated polyps can be classified with sufficient consistency to support current treatment recommendations | 185 serrated polyps extracted from the internal pathology database was searched for polypectomy specimens with a diagnosis containing the words "serrated," "hyperplastic polyp," (HP) "sessile serrated adenoma," (SSA) "sessile serrated polyp," and "traditional serrated adenoma" (TSA) removed between July 2003 and June 2005

Boston, USA | Number of polyps classified as HP, SSA, or TSA.

Diagnostic agreement between pathologists assessed by kappa statistic | 1st round Complete Agreement 82/185 (44%) k=0.55

Concordance Among Observers (k Value) 1st round (no clinical information provided) <10 mm: 0.40 (right) 0.51(left) >10 mm: 0.48 (right) 0.65 (left) Overall k=0.55

2nd round (clinical information provided) <10 0.28 (right) 0.50 (left) >10 0.36 (right) 0.68 (left) Overall k=0.48

3rd round after the consensus conference <10 0.46 (right) 0.61 (left) >10 0.41 (right) 0.46 (left) Overall k=0.58

Concordance on Each Category (k Value) TSA 1st round 0.80954 2nd round 0.78457 3rd round 0.83148 SSA 1st round 0.45508 2nd round 0.32352 3rd round 0.47823 HP 1st round 0.51996 2nd round 0.42231 3rd round 0.47823 Overall 1st round 0.55679 2nd round 0.46922 3rd round 0.58142 | V

Interobserver agreement for the diagnosis of serrated polyps appears moderate. Concordance for HP and SSA was moderate whereas it was nearly perfect for TSA. Providing information on polyp site and size did not improve concordance (second round). All observers relied more often on architectural features than on cytological ones to distinguish SSA from HP and agreement was reached that architectural features should provide the basis for the diagnosis of SSA. After this consensus interobserver concordance was slightly improved but remained moderate (k=0.58). |

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Higuchi 2005	Differential diagnosis	Cross-sectional study	891 conventional adenomas (AD), 298 hyperplastic polyps (HP), 27 sessile serrated adenoma (SSA), 10 (mixed polyp) MP and 24 traditional serrated adenoma (SA) obtained from patients during colonoscopic examination. 58.7% males mean age of patients was 63.8 ± 11.6 years in males and 60.9 ± 13.3 years in females (P = 0.0003). Montreal, Quebec, Canada	To determine clinicopathological features of serrated adenoma (SA), mixed polyp (MP) and the recently recognized sessile serrated adenoma (SSA)	TA (tubular adenoma) 688 (55.0%) TVA (tubulovillous adenoma) 190 (15.2%) VA (villous adenoma) 13 (1.0%), HP (hyperplastic polyps) 298 (23.8%) SSA 27 (2.2%) MP 10 (0.8%) SA (1.9%) SSA were more likely to be located in the right colon compared with AD or HP (P <0.05, P ¼ 0.003, respectively. No significant differences in gender distribution for HP, AD and ASP	**V** This study found the frequency of SSA to be approximately 2% of all polyps removed colonoscopically. SSA differ from other serrated polyps of colorectum in terms of location, morphology and immunophenotype.

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Torlakovic 2003	Differential diagnosis	Cross-sectional study	289 endoscopic biopsies of serrated polyps (SPs) from the large intestine located in the files of the Department of Pathology, Norwegian Radium Hospital all serrated polyps with various degrees of maturation/differentiation Oslo, Norway	Number of abnormal polyps	289 SPs, there were 243 polyps in the left colon and rectum and 46 polyps in the right colon Right colon Normal: 29 (63) Abnormal: 17 (37) Left colon Normal: 209 (85) Abnormal: 34 (15) p <0.001 (Fisher's Exact Test	**V** The overall percentage of polyps with abnormal proliferation was 18% We recommend evaluation of the localisation, size, and morphologic features when serrated polyps are included in colorectal carcinogenesis research

Author, publication year	Compared Interventions	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Goldstein 2003	Hyperplastic-like polyps that preceded microsatellite-unstable adenocarcinomas versus incidental hyperplastic polyps	Case controlstudy	Study group: 106 hyperplastic-like polyps that preceded 91 same-site, microsatellite-unstable adenocarcinomas mean and median patient ages were 68.2 and 69.5 years, respectively (range, 52.9-82.8 years; SD, 6.1 years). Control group: selected randomly from a large pool of patients with rectal or sigmoid, solitary, hyperplastic polyps completely resected. Mean and median ages at polypectomy were 64.1 and 64.0 years, respectively (range, 55.7-75.6 years; SD, 5.4 years). USA	Identification of distinguishing morphologic criteria of hyperplastic-like polyps that preceded microsatellite-unstable adenocarcinomas versus incidental hyperplastic polyps	<u>Study group</u> polyps had an expanded crypt proliferative zone, a serrated architectural outline that became apparent in the basilar crypt regions, basilar crypt dilation, inverted crypts, and a predominance of dysmaturational crypts (crypts with minimal cell maturation). <u>Control group</u> polyps had a proliferative zone confined to the basal crypt region, serrated architecture that became apparent in the superficial crypt region, rare to no basilar crypt dilation, and rare or no dysmaturational crypts.	**IV** Hyperplastic-like polyps that preceded microsatellite-unstable adenocarcinomas had a distinctive constellation of morphologic features related to altered and decreased cell function and control that resulted in dysmaturational crypts. This morphologic features provide initial guidelines to identify this potentially important subset of premalignant serrated-like polyps

7.11 Additional evidence tables prepared after December 2009

1. Nascimbeni R, Burgart LJ, Nivatvongs S & Larson DR (2002), Risk of lymph node metastasis in T1 carcinoma of the colon and rectum, *Dis.Colon Rectum*, vol. 45, no. 2, pp. 200-206.

2. Tominaga K, Fujinuma S, Endo T, Saida Y, Takahashi K & Maetani I (2009), Efficacy of the revised Vienna Classification for diagnosing colorectal epithelial neoplasias, *World J Gastroenterol.*, vol. 15, no. 19, pp. 2351-2356.

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Nascimbeni R., 2002	Patients with sessile T1 adenocarcinoma who underwent a colorectal resection.	To study the risk factor for lymph node metastasis in T1 carcinoma of the rectum. Retrospective cohort	Clinical records of 353 patients (median age: 68 (range, 36-95); 204 men, 149 women) with sessile T1 adenocarcinoma who underwent a colorectal resection from 1979 to 1995. N=353	Risk of lymph node metastasis for depth of submucosal invasion, lymphovascular invasion and site of carcinoma.	**Lymph Node metastasis rate, n(%)** 46(13) **Risk of lymph node metastasis, n(%)** Depth of submucosal invasion Sm1 (upper-third)=2 (3) Sm2 (middle-third)=9 (8) Sm3 8lower-third)=35 (23) In nine patients the depth could not be evaluated Lymphovascular invasion (LVI) Absent=37 (11) Present=9 (32) Site of carcinoma in the rectum Lower 1/3= 10(34) Middle 1/3= 6(11) upper 1/3= 3(8) **Significant predictor of lymph node metastasis, OR (95%CI) _p_:** Sm3 vs sm1, OR= 5.0 (2.3-10.6), p<0.001 LVI (+) vs LVI (-) OR= 3.5 (1.4-8.9), p<0.009 Lower 1/3 rectum vs higher rectum and other colonic segments OR= 6.0 (2.0-14.2), p<0.001	**III** T1 colorectal carcinomas with sm3 depth of invasion, lymphovascular invasion and location in the lower third of the rectum have a high risk of lymph node metastasis. These lesions should have an oncologic resection. In a case of the lesion in the lower third of the rectum, local excision plus adjuvant chemoradiation may be an alternative.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage.

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Tominaga K., 2009	Patients who performed colonoscopie, sigmoidoscopies or proctoscopies at Toho university Ohashi medical center (Tokyo) between January 2001 and December 2003. Japan	To prospectively investigate the efficacy of the revised Vienna Classification for diagnosing colorectal epithelial neoplastic lesions in cold biopsy specimens. Diagnostic accuracy study with prospective recruitment Reference standard: WHO classification	171 patients (93 men,78 women, mean age.66.9years; range 33-93) with colorectal epithelial lesions that were not considered suitable for direct endoscopic resection.	Sensitivity, specificity, PPV and NPV	**Epithelial lesion, N** 1 lesion: 165 2 lesions: 5 4 lesions: 1 Total number of lesion: 179 399 cold biopsy specimens (5 inadequate specimens excluded from the analysis) **Efficacy of revised Vienna Classification in cold biopsy specimens** Intramucosal lesion vs submucosal invasive carcinomas: Sensitivity: 22.2%(95% CI:3.0-41.4) PPV:100% Specificity:100% NPV: 71.4%(95% CI:58.8-84.1) Intramucosal lesion vs lesions invasive to the submucosa or beyond: Sensitivity: 59.7%(95% CI:51.7-67.7) PPV:100% Specificity:100% NPV: 37.6%(95% CI:27.7-47.4)	**III** The revised Vienna Classification for cold biopsy specimens has high positive predictive value in the diagnosis of colorectal carcinoma invasive to the submucosa or beyond.

Quality assessment: prospective recruitment, spectrum of patients representatives of the patients who will receive the test in practice; patients selection criteria clearly described; same reference standard for all patients; execution of the index test clearly described; execution of the reference standard clearly described; the index test results interpreted without knowledge of the results of the reference standard: not reported; uninterpretable /intermediate test results reported; no withdrawal.

8
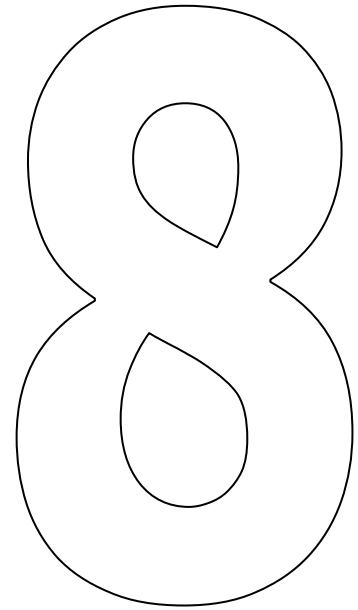
Management of lesions detected in colorectal cancer screening EVIDENCE

EU CRC Guidelines Literature Group

8.1 Management of lesions detected in colorectal cancer screening

8.1.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 1

How should polyps be treated (criteria for endoscopic or surgical removal) ?

PICOS

P: All individuals with polyps
I: Polypectomy
C: Surgery
O: Complete excision, recurrence and adverse events
S: Any study

SEARCH METHOD

Searches were conducted for primary studies on MedLine, Embase and for systematic reviews on The Cochrane Library including only studies published between 2000 and 2008

Medline and Embase:

polypectomy AND endoscopy AND management AND small polyps
polypectomy AND colorectal neoplasms AND endoscopic treatment
polypectomy AND rectal polyps AND criteria for endoscopic treatment
polypectomy AND colorectal neoplasms AND complete excision
polypectomy AND colorectal polyps AND surgical removal
polypectomy AND colorectal polyps AND laparoscopic removal
[Mesh] colorectal neoplasms AND colorectal surgery AND recurrence
[Mesh] endoscopy, gastrointestinal AND colonic polyps AND safety
pedunculated adenomas AND management
colonoscopy AND snare electrocoagulation

<u>Cochrane Library:</u>

We searched for Cochrane Reviews among the reviews published by the Colorectal Cancer Review Group.

We also looked at the references of retrieved articles to find other relevant paper.

RESULTS

No systematic reviews were found on endoscopic mucosal resection for colorectal polyps. One SR was found on transanal endoscopic microsurgery (1)

We found 14 articles on endoscopic mucosal resection for sessile or pedunculated colorectal polyps (2-15) and 4 on transanal endoscopic microsurgery (16-19).

All but one (12), which is an RCT, were uncontrolled case series.

The results are reported descriptively and summarized in the tables below. Table 1 reports the results of colorectal polypectomy, table 2 reports the results of transanal endoscopic microsurgery.

In table 1 are reported also the results of studies published before 2000, not included in our search but reported in the paper of Perez Roldan.

The results of studies on TEM will be reported in a separate summary document

Jameel 2006 (2) assessed the safety and efficacy of endoscopic mucosal resection (EMR) in an uncontrolled series of 24 patients with large polyps (1-5 cm). 33 EMR on 30 lesions were performed. 17 were sessile, 6 pedunculated and 7 flat lesions. Due to diathermy artefact, the completeness of excision could not be stated on histology in 19 lesions. However, the endoscopist was satisfied that macroscopic clearance had been achieved in all these cases. Only one lesion could not be completely excised. Two cases of bleeding were reported and no perforation. With a median follow up of 21 months no case of recurrence of the 7 cases of adenocarcnoma was seen.

Stergiou 2003 (3) reported the results of a consecutive series of 68 patients with large polyps over than 30 mm in diameter (27 peduncolated, 41 sessile) treated with snare polypectomy. He found that piecemeal resection was used significantly more often in sessile polyps (38/41, 93%) than in pedunculated polyps (4/27, 15%), that follow-up colonoscopy after 3 months showed remaining adenomatous tissue in 14 cases of piecemeal-resected polyps (28%) but in no case of resected pedunculated polyps, and that a second procedure was necessary in 12/41 cases in sessile polyps, 18%, vs. 0/27 cases in pedunculated polyps. He concluded that endoscopic snare resection of giant colonic polyps is a safe procedure, and that secondary operative management due to coexisting malignancy of the polyps is rarely necessary. For the removal of sessile polyps piecemeal, resection is often necessary.

Church 2003 (4) reported the results of a series of 252 patients with polyps larger than 2 cm treated in the first instance endoscopically. The study reported the rate of complication, need for surgery and presence of residual polyps at follow up according of polyp size, site and shape. The study found that polyp shape, size and location all influence the success of endoscopic polypectomy. Polyps >30 mm in maximum diameter are significantly more advanced histologically but also significantly more difficult to treat successfully than those <30 mm. Pedunculated polyps are much easier to remove completely than sessile polyps; flat lesions are the most difficult of all to remove completely and tend to be more common in the right colon. The right colon, especially the caecum, is more thin walled that the left. This translates into higher rates of complications after removing polyps from the right colon than the left. These results should be considered with caution because the factors have been considered separately and a multivariate analysis has not been performed.

Boix 2007 (5) reported the results of a case series of 74 patients with a total of 74 sessile polyps larger than 4 cm that were removed endoscopically using argon plasma coagulation (APC) as an adjunct to piecemeal technique. Surgery was recommended in patients with invasive neoplasia. 40.8% of polyps were completely removed in one session, 29.6% in two sessions, and 29.6% required more

than three sessions. The mean number of polypectomy sessions per patient was 2.25 and was not related to polyp size. Complementary APC was necessary in 59.25%. During follow-up, recurrence occurred in one patient with LGD (3.2%) and four patients with HGD (17.4%); they were successfully retreated endoscopically with APC (delayed APC) in a single session. No significant association was observed between polyp size and recurrence.

The recurrence rate was similar regardless of whether or not APC was used to complete the endoscopic resection. Bleeding was the only postpolypectomy complication, occurring in 13.5% of patients. Authors concluded that excision of these large sessile polyps was feasible with a standard technique without saline injection and that APC was an effective adjunct to piecemeal polypectomy.

Brandimarte 2001 (6) reported the result of a case series of 35 patients with pedunculated polyps 3 cm or larger treated with polypectomy performed in two step: first a polypectomy snare was placed around the middle of the stalk as a prophylactic measure to prevent bleeding, then the colonoscope was taken out without removing the snare after dismantling it and blocking with a clip.

Endoscopic polypectomy was done using a second snare and transecting the stalk of the polyp at 2 mm above the first snare. The first snare was left in place and the patient was discharged within 3 hours. It sloughed off spontaneously, being evacuated within 4 days. All the polypectomies were completed and there were no cases of complications or of recurrence at 6 months follow up.

Dell'Abate 2001 (7) reported the results of a case series of 97 patients with 104 gyant polyps (size 3 cm or larger) treated endoscopically. Polypectomy was performed with standard endoscopic snare technique using coagulation current. Excision was completed in 74.6% of cases. Complications occurred in 3% and recurrence in 3% of cases. Polypectomy was completed in one session in 58% of patients (pedunculated 90%, short-stalked: 55%, sessile 17%. The remaining polyps, mainly sessile, were excised by a piecemeal technique in a mean of 2.2 (range, 1-4) sessions. Authors concluded that polypectomy of giant colorectal polyps, performed by an expert endoscopist, is feasible, effective, and safe, even on an outpatient basis. The authors confirm that malignant polyps with incomplete excision, lymphovascular invasion, and poor differentiation require bowel resection.

Doniec 2003 (8) reported the results of a case series of 184 patients with sessile (76%) or pedunculated (24%) polyps larger than 3 cm (mean diameter 4.7) treated endoscopically. Sessile adenoma were treated by piecemeal technique. All adenoma were completely removed. All pedunculated adenomas were removed in one session; 11% of sessile adenomas required more than one session. Complication occurred in 13% of cases. There was 1 case of perforation (0.5). At a mean of 40 months of follow up the recurrence of adenoma was 3% and 0.5% for carcinoma. Authors concluded that endoscopic polypectomy/mucosectomy for large colorectal polyps is a difficult method of treatment, although it is safe in experienced hands and prevents patients from undergoing unnecessary surgery

Perez Roldan (9) reported the results of a case series of 142 patients with 147 polyps (50% sessile) greater than 2 cm treated by endoscopic polypectomy. Completion of resection was achieved for 100% of pedunculated polyps and for 93.3% of sessile polyps. Haemorrage occurred in 5.4% of cases and perforation in 1.3%. Recurrence at a mean of 43 months of follow up was 1.3%. Authors concluded that the endoscopic resection of large polyps (≥2 cm in size) is a technique that is safe, effective, and less expensive than surgery, though not free from complications. It entails a high percentage of complete resections, and a low number of relapses when performed using the right technique, along with a low frequency of complications. It should be considered the technique of choice for the treatment of these types of polyps except for those including an invasive carcinoma.

Garcia 2004 (10) reported the results of a case series of 22 patients with flat (50%) or sessile adenomas(50%) treated with argon plasma coagulation only (for flat adenomas) or with piecemeal technique followed by APC for sessile adenomas. Completion of resection was of 96% with a mean number of 1.7 treatment sessions. Recurrence appeared in 20% of patients and as not related to the kind of treatment (only APC or APC+ piecemeal) but to the size of polyp. There were no major complications. Authors concluded that argon plasma coagulator ablation of flat colorectal adenomas is an efficacious and safe technique, specially in the right colon, but results must be confirmed in

controlled trials with a higher number of patients. APC is also a safe technique for the removal or residual tissue after incomplete polypectomy

Katsinelos 2008 (11) reported the results of a case series of 17 patients with peduncolated polyps of at least 1 cm diameter and a stalk diameter ≤4 mm treated with endoclipping of the stalk before resection. Completion of resection was obtained in all cases. Only one case of complication (5.9%) was seen (postcoagulation syndrome). No cases of recurrence were seen at a mean of 14 months follow up. The study reported also the results of two other studies:

Iida 1994 reported the clipping method in 40 colorectal polyps (6 sessile, 10 semipedunculated, and 24 pedunculated) with a mean size of polyp head being 10±5mm (range, 4 to 23 mm). No postpolypectomy bleeding or perforation occurred. The second study (Cipolletta 1999) included only 4 large pedunculated colonic polyps, whose head size ranged between 3 and 6 cm. Authors concluded that the technique described could be recommended as an alternative to endoloop ligation for a safe resection of pedunculated colorectal polyps having a stalk diameter <4mm or as the method of choice for safe removal of selected large pedunculated polyps in which endoloop ligation is impossible. However, whether this technique is safer than conventional methods in large pedunculated colorectal polyps awaits results from randomised controlled studies.

Iishi 2000 (12) reported the result of a case series of 56 patients with sessile colorectal polyps at least 2 cm in diameter treated with en bloc resection or piecemeal technique. 25% of polyps were treated by en bloc resection. Completion of resection was obtained in all cases, but residual tumour was found within 1 year follow up in 50% of cases treated by piecemeal technique. After the second treatment 38 % of cases still have residual tumour and 40% after the third. Overall, 100% of cases treated by en bloc resection have been cured and 83% of patients treated by piecemeal. Authors concluded that endoscopic piecemeal resection after submucosal saline injection with an intensive follow-up care program is thus a safe and effective treatment for large sessile colorectal polyps.

Hsieh 2001(13) performed a randomised controlled trial comparing epinephrine submucosal injection before polypectomy vs no injection in 129 subject undergoing polypectomy. 57% of polyps were <1 cm and 42% were located in the stomach. The study found a statistically significant reduction of immediate bleeding in the epinephrine group. No difference were found in the frequency of delayed bleeding and perforation.

Arebi 2007(14) reported the results of a case series of 161 patients with sessile (66%) or flat adenoma ≥ 2cm in diameter treated with EMR using the "inject and cut" technique, a variation of the strip biopsy technique. Clearance after the first procedure was of 60%. Total endoscopic clearance success rate after up to six procedure was of 95.4%. Recurrence requiring surgery was of 4.6%. Bleeding requiring hospitalisation happened in 5.7% of cases. Authors concluded that with careful attention to technique, piecemeal EMR is a safe option for the resection of most sessile and flat colorectal polyps ≥20 mm in size. A stricter follow-up may be required for larger lesions because of a higher risk of recurrence.

Bergmann 2003 (15) reported the results of a case series of 57 patients with 71 flat or sessile adenoma larger than 1 cm treated by endoscopic mucosal resection. Completion of resection was of 94% with no difference between en bloc or piecemeal resection. Bleeding and perforation occurred in one case each. Recurrence occurred in 2.8% of patients. Authors concluded that advanced non-polypoid colorectal adenomas and early-stage carcinomas can be safely and effectively resected by endoscopic mucosal resection.

CONCLUSIONS

Many studies have been retrieved assessing the safety and efficacy of endoscopic mucosal resection for colorectal polyps large up to 5 cm but all are uncontrolled case series. Only one RCT compared epinephrine submucosal injection before polypectomy vs no injection in 129 subject undergoing polypectomy has been located. In all the case series peduncolated polyps are removed by snare polypectomy and sessile by piecemeal resection. Peduncolated polyps are easier to remove by snare

polypectomy and the rate of cure are higher. Sessile or flat adenoma removed by piecemeal resection often followed by argon plasma coagulation need often more than one treatment and have a lesser cure rate. Overall cure rate ranges from 72% to 100% in the more recent series (published since 2000). Recurrence range from 0 to 9.2% in the more recent series (published since 2000). Recurrence is significantly higher in the oldest series. Bleeding occurred in 0 to 18% of cases and perforation on 0 to 1.4%. (LEVEL OF EVIDENCE V)

Results from one RCT showed that epinephrine submucosal injection is efficacious in reducing immediate bleeding after polypectomy (LEVEL OF EVIDENCE II)

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8.1.2 Evidence tables

Table 1. Case series on colorectal polypectomy

AUTHOR	PEDUNCOLATED	SESSILE	TOTAL	INTERVENTION	HAEMORRAGE	PERFORATION	CURED	RELAPSED
Jameel 2006	6	17 7flat	30 1-5 cm	Adrenaline injection, diatermic snare in 1 section or piecemeal, then APC	6.6%	0	97.7%	0
Stergiou 2003	27	41	68 larger than 3 cm	Adrenaline injection, diatermic snare in 1 section or piecemeal, then APC	18%	0	72%	
Church 2003	65	163 65 flat	311 larger than 2cm	Snare polypectomy, 1 section or piecemeal	6.5%	0	77.7%	
Boix 2007		54	54 larger than 4 cm	Piecemeal + APC	13.5%	0	100%	9.2%
Brandimarte 2001	43		43 larger than 3 cm	Two snare	0	0	100%	0
Dell'Abate 2001	49	35 20 flat	104 larger than 3 cm	Diathermic snare for peduncolated, piecemeal for sessile	3.8%	0	74.6%	3%
Doniec 2003	45	141	186 larger than 3 cm	Snare for peduncolated, piecemeal +APC for sessile	15%	0.5%	100%	3%
Pérez Roldán 2004	73	74	147 larger than 2cm	Adrenaline injection, diathermic snare in 1 section or piecemeal, then APC	5.4%	1.3%	96.6%	1.3%
Garcia 2004		11 11 flat	22 larger than 2 cm	Piecemeal +APC for sessile, APC alone for flat	0	0	90.9%	2'%
Katsinelos 2008	17		17 larger than 1 cm	Endoclipping + diathermic snare	0	0	100%	0%
Iishi 2000		56	56 larger than 2 cm	piecemeal	7%	0	91.5%	
Arebi 2007	55	106	161 larger than 2 cm	"inject and cut"	5.7%	0	95.4%	4.6%

AUTHOR	PEDUNCOLATED	SESSILE	TOTAL	INTERVENTION	HAEMORRAGE	PERFORATION	CURED	RELAPSED
Bergmann 2003		71 sessile or flat	71 larger than 1 cm	en bloc snare or endoscopic aspiration mucosectomy or piecemeal	1.4%	1.4%	94%	2.8%
Binmoeller 1996	47	129	176		24%	0	76%	16%
Walsh 1992		117	117		8.5&	0.8%	88%	28%
Zlatanic 1999		77	77		6.5%	1.3%	45.5%	54.5%
Kanamori 1996		33	33		9.1%	0	100%	0
Bedogni 1986	2.	42	66		3.1%	0	87.9%	11%
Webb 1985	72	30	102		7.8%	0		
Nivatvongs 1986	196	84	280		0.7	0		

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Jameel 2006	To assess safety and efficacy of endoscopic mucosal resection (EMR) for large colorectal polyps retrospective case series USA	24 patients who received EMR out of 87 patients who underwent endoscopic polypectomy for polyps in sizes ranging from 10 mm to 50 mm performed under 2 experienced endoscopists registered on a database of an endoscopy unit Median size of 30 polyps resected by EMR was 20 mm with the largest being a 50 mm pedunculated polyp in the sigmoid colon. 56.6% of the polyps were located in the rectum or sigmoid 6.7% were located in the descending colon, 10% in the transverse colon and 26.7% in the ascending colon. These were categorized into 17 sessile, 6 pedunculated and 7 flat lesions.	Endoscopic mucosal resection (EMR)	Completion of excision Complication recurrence	21 months	33 EMRs were performed on 30 lesions in 24 of these patients. Adenocarcinoma was found in 7 lesions, of which 6 were intramucosal and 1 was invasive. Completion of excision: Due to diathermy artefact, the completeness of excision could not be stated on histology in 19 lesions. However the endoscopist was satisfied that macroscopic clearance has been achieved in all these cases. Only one lesion could not be completely excised. Complication: 2 cases of bleeding; perforation: none Recurrence: none of the patients diagnosed with adenocarcinoma have shown any sing of recurrence	**V** EMR is a safe procedure. It is effective in the resection of early cancers and polyps not suitable for conventional polypectomy..

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Stergiou 2003	To determine whether complete snare resection of giant colonic polyps (at least greater than 30 mm) is feasible and safe and to evaluate how often surgery is necessary due to invasive cancer detected histologically after polypectomy. case series Germany	59 consecutive patients with 68 colonic polyps larger than 30 mm in diameter (27 peduncolated, 41 sessile). Six patients were excluded because of submucosal infiltration revealed by endosonography.	Snare polypectomy was performed after an endoscopic ultrasound with a miniprobe found no sign of invasive, or, depending on the appearance of the polyp, a bleeding prophylaxis had been carried out. Acute procedural or delayed bleeding was treated endoscopically.	Completion of resection Need of a second procedure complications	3 months	26 polyps, mostly pedunculated were resected en bloc (38%) and histologically confirmed as completely resected. 42 polyps had to be resected by piecemeal technique (62%). Piecemeal resection was used significantly more often in sessile polyps (38/41, 93%) than in pedunculated polyps (4/27, 15%, $P<0.01$). Completion of resection: Follow-up colonoscopy after 3 months showed remaining adenomatous tissue in 14 cases of piecemeal-resected polyps (28%) but in no case of resected pedunculated polyps ($P<0.01$). Need of a second procedure : 12/41 cases in sessile polyps, 18%, vs. 0/27 case in pedunculated polyps, $P<0.05$). Complications: Acute bleeding: 18%; 10 sessile polyps, 2 pedunculated polyps, $P<0.05$) . Delayed bleeding (after 2–5 days) :4%, No need for blood transfusion. No perforation occurred.	V Endoscopic snare resection of giant colonic polyps is a safe procedure, and that secondary operative management due to coexisting malignancy of the polyps is rarely necessary. For the removal of sessile polyps piecemeal resection is often necessary.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Church 2003	The purpose of the present study is to describe a large consecutive series of colonic polyps evaluated endoscopically and to determine which factors about the polyps influence the ability to perform a safe and effective endoscopic polypectomy. case series USA	252 patients with 311 polyps larger than 2 cm.	Polyps were removed with regular- or mini-sized oval snares from a variety of manufacturers, using pure coagulation current and a variety of electrocautery machines. Polyp fragments were suctioned out on the end of the scope, removed in a basket or aspirated through the suction channel into a trap..	Need for surgical resection, complications persistence of the index polyp at follow up according to size, polyp shape, location	Not reported	70% of the polypectomies were performed piecemeal and adrenaline injection was used in 33 cases (13%). There were 19 polyps containing invasive cancer, 14 of which needed surgical resection because of unfavourable characteristics <u>Need for surgery according to polyp size:</u> 2-3 cm: 14.7% 3,1-4 cm: 27.7% 4,1-5 cm: 31% 5.1-6 cm: 33.3% >6 cm: 50% Total 21.2% <u>Need for surgery according to polyp shape:</u> Flat:20.9% Sessile 55.6% Peduncolated: 23.5% <u>Need for surgery according to polyp location</u> Caecum: 27.7% ICV: 75% Ascending: 10% Hepatic flexure: 15% Transverse: 6.3% Splenic flexure:36.4% Descending 14.3% Sigmoid: 21.8% <u>Residual polyps according to size:</u> 2-3 cm: 10.9% 3,1-4 cm: 35.3% 4,1-5 cm: 32.3% 5.1-6 cm: 25% >6 cm: 100% Total: 22.3%	V Polyp shape, size and location both influence the success of endoscopic polypectomy. Polyps >30 mm in maximum diameter are significantly more advanced histologically but also significantly more difficult to treat successfully than those <30 mm. Pedunculated polyps are much easier to remove completely than sessile polyps; flat lesions are the most difficult of all to remove completely and tend to be more common in the right colon. The right colon, especially the caecum, is more thin walled that the left. This translates into higher rates of complications after removing polyps from the right colon than the left.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
						Residual polyp according to polyp shape: Flat:53.3% Sessile 40.6% Peduncolated: 0% Residual polyp according to location: Caecum: 38.2% ICV: 50% Ascending: 25% Hepatic flexure: 14.3% Transverse: 30.8% Splenic flexure:60% Descending 13.3% Sigmoid: 19 % Complications of polypectomy: 6.5% No significant difference for size , shape; more frequent in the ascending colon (7.4%) than in the transverse (0%) or descending (2.6%)	

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Boix 2007	To determine the safety and effectiveness of endoscopic removal of sessile colorectal adenomas larger than 4 cm. case series Spain	74 patients with a total of 74 sessile polyps larger than 4 cm	Polyps were Removed endoscopically using argon plasma coagulation (APC) as an adjunct to piecemeal technique. Surgery was recommended in patients with invasive neoplasia..	Number of polypectomy session, complications recurrence	6 months	Twelve patients (16.2%) underwent surgery because of invasive neoplasia at histology . 8 patients lost at follow up. 22 polyps (40.8%) were completely removed in one session, 16 (29.6%) in two sessions, and 16 (29.6%) required more than three sessions. The mean number of polypectomy sessions per patient was 2.25 and was not related to polyp size. Complementary APC was necessary in 59.25%, 70 sessions of APC being necessary (mean,2.18 sessions per patient), 26 at initial polypectomy and 44 in a subsequent procedure. During follow-up, one patient with LGD (3.2%) and four patients with HGD (17.4%) recurred and were successfully retreated endoscopically with APC (delayed APC) in a single session. No significant association was observed between polyps size and recurrence. The recurrence rate was similar regardless of whether or not APC was used to complete the endoscopic resection. Bleeding was the only postpolypectomy complication, occurring in 13.5%, using APC	**V** Excision of these large sessile polyps was feasible with a standard technique without saline injection and that APC was an effective adjunct to piecemeal polypectomy. Endoscopic snare polypectomy performed by an expert endoscopist is safe and effective, and should be considered the treatment of choice for all LGD or HGD large sessile colorectal polyps. These procedures can be performed on an outpatient basis.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Brandimarte 2001	To assess safety and efficacy of snare excision of large peduncolated polyps case series Italy	35 patients with 43 peduncolated polyps of benign appearance and size of 3cm or larger (range 3-5 cm)	Polypectomy performed in two step: first a polypectomy snare was placed round the middle of the stalk as a prophylactic measure to prevent bleeding, then the colonoscope was taken out without removing the snare after dismantling it and blocking with a clip. Endoscopic polypectomy was done using a second snare and transecting the stalk of the polyp at 2 mm above the first snare. The first snare was left in place and the patient was discharged within3 hours. It sloughed off spontaneously, being evacuated within 4 days.	Completion of excision Complication recurrence	6 months	Completion of the excision: all Complication: none Recurrence: none	**V** This technique is safe and effective to remove peduncolated polyps larger than 3 cm

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Dell'Abate 2001	To assess feasibility, safety and effectiveness of endoscopic treatment of polyps of size 3 cm or larger retrospective review of case series Italy	97 patients with104 gyant polyps (size of 3cm or larger)	Polypectomy performed with standard endoscopic snare technique using coagulation current. For pedunculated and short-stalked polyps the diathermic snare was placed around the stalk of the polyp and resection was completed, in the majority of cases, at the same time. A piecemeal technique was used for the polypectomy of sessile polyps and short-stalked polyps with a large stalk or localized on the right colon. For this kind of polyp, the diathermic snare was placed around the most accessible part of the polyp and gradually- closed until separation was complete. After a first portion of the polyp had been excised, the snare was placed around an adjacent segment and down to the muscularis mucosae until most of the polyp was removed	Completion of excision n. of session required Complication recurrence	Median: 38 months	pedunculated: 47%, short-stalked: 19 %, sessile: 34% Mean size of the lesions: 3.41 cm, with 21 polyps more than or equal to 4 cm and a maximum size of 7 cm. snare polypectomy performed in one session: pedunculated polyps: 90% short-stalked polyps: 55 % sessile polyps:17 % total 58%. The remaining 43 polyps (29 sessile, 9 short stalked, and 5 pedunculated) were excised by a piecemeal technique in a mean of 2.2 (range, 1-4) sessions. Completion of the excision: 74.6% Complication: 3.8% Recurrence: 3%	**V** Polypectomy of giant colorectal polyps, performed by an expert endoscopist, is feasible, effective, and safe, even on an outpatient basis. The authors confirm that malignant polyps with incomplete excision, lymphovascular invasion, and poor differentiation require bowel resection. Postpolypectomy surveillance is useful for all patients who have undergone colonoscopic resection of giant adenomatous or malignant polyps

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Doniec 2003	To evaluate the capabilities and risks of endoscopy in complete removal of large (<3cm) colorectal polyps. retrospective case series Germany	184 patients with 186 colorectal polyps larger than 30 mm in diameter.	Sessile polyps were resected using a piecemeal Technique. The aim of resection was to shave off polyp tissue as far as the muscularis propria. If complete removal with the snare was not possible the remaining tissue was coagulated using an argon plasma coagulator. Peduncolated polyps were removed with a snare excision. An initial attempt was made to remove the pedunculated polyp in one piece by resecting the proximal half of the stalk. If this was not possible, the head of the polyp was shaved down to a size allowing a snare to be placed around the residual portion, and single resection of the stalk was performed.	Completion of resection Need of a second procedure complications	Mean 40 months	Mean diameter: 4.7 cm Sessile: 76% Peduncolated: 24% <u>Completion of resection</u>: all sessile and pedunculated polyps. None of the patients with invasive carcinoma who underwent surgical resection (n 10) had any evidence of tumour in the resected specimen. <u>Need of a second procedure</u> Peduncolated polyps: none Sessile: 11% <u>Complications</u>: haemorrhage during polypectomy: 13%; Delayed haemorrhage: 2% Perforation: 0.5% <u>Recurrence:</u> adenoma: 3% Carcinoma: 0.5%	**V** Endoscopic polypectomy/ mucosectomy for large colorectal polyps is a difficult method of treatment, although it is safe in experienced hands and prevents patients from undergoing unnecessary surgery. The risks of perforation or bleeding are not significantly different from those in polypectomy of "normal-sized" polyps.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Perez Roldan 2004	To analyse the efficacy and complications of colonoscopic polypectomy of large colorectal polyps retrospective case series Spain	142 patients with 147 colorectal polyps larger than 20 mm in diameter.	Injection of diluted adrenaline -1:10,000- at the base of the pedicle, or a submucosal injection for sessile polyps. If a sessile polyp was larger than 3 cm it was raised with saline to a variable volume. It was then resected with a diathermic snare, in one fragment if possible, or otherwise with the smallest possible number of fragments (piecemeal resection), with a later attempt to recover them all. Remnant adenomatous tissue was fulgurated with an argon plasma coagulator. An injection of diluted epinephrine at a concentration of 1:10,000, and occasionally an endoloop for pedunculated polyps, was used as a prophylactic measure to prevent postpolypectomy bleeding	Completion of resection Need of a second procedure complications	Mean 43 months	Diameter less than 3cm: 50.3% 3-3.9 cm: 20.4% 4-4.9 cm: 14.3% ≥5 cm: 15% Sessile: 50% Peduncolated: 50% Completion of resection: pedunculated polyps 100% There was no tumoural invasion of the pedicle in any of the cases. Sessile polyps:93.3%. Overall, five patients required surgery Need of a second procedure Peduncolated polyps: none Sessile: average number of colonoscopies 1.35 ± 0.6 (range, 1-4). Complications: haemorrhage 5.4% Perforation: 1.3% Recurrence: 1.3%	V The endoscopic resection of large polyps (≥2 cm in size) is a technique that is safe, effective, and less expensive than surgery, though not free from complications. It entails a high percentage of complete resections, and a low number of relapses when performed using the right technique, along with a low frequency of complications. It should be considered the technique of choice for the treatment of these types of polyps except for those including an invasive carcinoma, in which case the polyp is not completely resected and complications may appear. Such patients must be referred for laparoscopic for open surgery.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Garcia 2004	To evaluate argon plasma coagulation APC efficacy and safety in the treatment of flat and sessile colorectal adenomas prospective case series Spain	22 patients with colorectal polyps larger than 20 mm in diameter.	Flat or carpet like adeoma: argon plasma coagulation scheduled every 15 days until adenomatous tissue had completely disappeared Large sessile adenomas: first piecemeal polypectomy and then APC ablation of residual adenomatous tissue	Completion of resection Need of a second procedure complications	Mean 15 months	Mean Diameter :22 mm (range 20-40) Flat or carpet-like: 50% Sessile : 50% Completion of resection: 90.9% Need of a second procedure Mean number of session: 1.7 Complications: none Recurrence: 20% There was no relationship between recurrence and previous piecemeal polypectomy. Only 1 patient out of 10 (10%) who had been treated exclusively with APC recurred, and so did 3 patients (30%) who had been treated with both methods (p >0.05). Recurrence was related with the initial size of the adenomatous tissue to be treated	V Argon plasma coagulator ablation of flat colorectal adenomas is an efficacious and safe technique, specially in the right colon, but results must be confirmed in controlled trials with a higher number of patients. APC is also a safe technique for the removal or residual tissue after incomplete polypectomy

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Katsinelos 2008	Eo assess the safety and efficacy of endoclipping of the stalk before resection of large pedunculated colorectal polyps retrospective case series Grece	17 patients with colorectal polyps at least 10mm in diameter and stalk diameter ≤4 mm..	Endoclipping-assisted endoscopic polypectomy. Two or 3 clips were placed at the base of polyp's stalk. To ensure sufficient tightening, we observed the color of the head of the polyp changing to dark red after endoclipping. A diathermic snare was then used to sever the stalk of the polyp at least 5mm above the clips	Completion of resection complications	Mean: 14.5 months	The polyp head was >10mm in all patients, the largest being 22 mm. The diameter of the stalk was r4mm in 14 polyps (82.3%), the largest being 5.4 mm. Completion of resection: 100% Complication: No intraprocedural or late bleeding or perforation occurred. One patient (5.9%) developed postcoagulation syndrome (abdominal pain, fever 38.51C, and leucocytosis), because the snare touched the clips during transection. Recurrence: none	V The technique described could be recommended as an alternative to endoloop ligation for a safe resection of pedunculated colorectal polyps having a stalk diameter <4mm or as the method of choice for safe removal of selected large pedunculated polyps in whose endoloop ligation is impossible. However, whether this technique is safer than conventional methods in large pedunculated colorectal polyps awaits results from randomised controlled studies.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Iishi 2000	To evaluate the effectiveness of endoscopic piecemeal resection with submucosal saline injection for treatment of sessile colorectal polyps 2 cm or greater in diameter. retrospective case series Japan	56 patients with sessile colorectal polyps at least 2 cm diameter	Endoscopic resection was performed with a submucosal saline injection technique. When en bloc resection was not considered possible, lesions were removed in a piecemeal fashion by excising fragments larger than 10 mm in diameter	Completion of resection Number of session complications	Mean: 34 months	Size: range: 2-5 cm . Completion of resection: 100%. 25% polyps en bloc and 75% piecemeal. Complication:7% Recurrence: residual tumour found at follow up within 1 year En bloc resection: none Piecemeal: 53.6% after the first treatment; 38% after the second treatment, 40% after the third treatment. 4 cases (7%) underwent open colectomy after 1 or 2 treatment	V After a median follow-up period of 34 months (range 12 to 84 months), cure was ultimately achieved in 83% of patients with sessile colorectal polyps 2 cm or greater in diameter resected in a piecemeal fashion. Endoscopic piecemeal resection after submucosal saline injection with an intensive follow-up care program is thus a safe and effective treatment for large sessile colorectal polyps.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Hsieh 2001	To determine whether submucosal epinephrine injection before polypectomy could reduce the incidence of bleeding and perforation RCT Taiwan	129 consecutive patients with 175 sessile polyps. Exclusion criteria: patient with bleeding tendency (taking anticoagulants, platelet <50000/mm3, protrombin time less than 30%)	Experimental: epinephrine injection before polypectomy. (n.68, 75 polyps) Control: no epinephrine injection. (n.61, 76 polyps). 42% of polyps were located in the stomach	Immediate bleeding Delayed bleeding perforation	1 months	Polyps<1 cm:57% Polyps 1-2 cm: 34%. Total bleeding: epi: 2.6% ctrl: 9.2% P: NS immediate bleeding: epi: 1.3% ctrl: 9.2% P:0.03 delayed bleeding: epi: 1.3% ctrl: 0 perforation: epi: 1.3% ctrl: 1.3%	II Submucosal epinephrine injection is safe and effective in preventing immediate bleegind

Quality assessment: allocation concealment: adequate; blinding of provider: not possible; blinding of patients: not relevant; blinding of outcome assessment: not relevant (objective outcome); none lost at follow up.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Arebi 2007	To evaluate the efficacy and safety of EMR in the treatment of large sessile and superficially spreading polyps and to identify the factors related to recurrence and failure of the technique. Retrospective case series UK	161 patients with 161sessile or flat polyps measuring ≥ 20 mm in size	EMR was performed using the "inject and cut" technique, a variation of the strip biopsy technique	Completion of removal Recurrence complication	12 months	The majority of the polyps measured 20_29 mm (42%) and the mean size was 32.5 mm. Sessile: 66% <u>Clearance</u> after the first procedure 60% clearance after the second: 24% after the third: 9.4% after the fourth: 1.3% after the sixth 0.7%, Total endoscopic clearance success rate :95.4%. <u>Recurrence</u> requiring surgery: 4.6% There was a significant statistical association between size and recurrence (p< 0.001) Recurrence was not correlated to site of the polyp (p: 0.07). Recurrence was not correlated to polyp morphology Recurrence was not correlated to the severity of dysplasia <u>Complication:</u> Bleeding: 5.7% Perforation: 0	V With careful attention to technique, piecemeal EMR is a safe option for the resection of most sessile and flat colorectal polyps ≥20 mm in size. A stricter follow-up may be required for larger lesions because of a higher risk of recurrence.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Bergmann 2003	To evaluate the usefulness of EMR to treat flat and sessile colorectal neoplastic lesions. retrospective case series Germany	57 patients with 71 advanced non-polypoid (flat or sessile) colorectal adenoma >1 cm or early-stage carcinoma	A saline–epinephrine solution (saline 0.9%, epinephrine 0.001%) was injected into the submucosal layer using a 23-gauge needle. Lesions were then excised by snare resection (SR) using a combination of cutting and coagulation current. When SR could not be applied, e.g., because of location or size of the lesion, endoscopic aspiration mucosectomy (EAM) or EMR using a cap-fitted endoscope] was performed. If because of the size of the lesion piecemeal resection was planned, the lesion margin was marked by argon plasma coagulation (APC) prior to submucosal resection.	Completion of resection Complications Recurrence	Mean: 18 months	Mean tumour size 25.4 mm 1 adenoma 8 carcinoma <u>Completion of resection</u>: 94% <u>Complication:</u> perforation: 1(1.4%) Bleeding: 1(1.4%) <u>Recurrence</u>: 2.8%	**V** Advanced non-polypoid colorectal adenomas and early-stage carcinomas can be safely and effectively resected by endoscopic mucosal resection.

8.2   Management of pT1 cancers

8.2.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 2

How should malignant polyps (T1 – carcinomas) be treated (criteria for completion surgical resection)?

PICOS

P: All patients with malignant polyps (T1 carcinomas)
I: Polypectomy
C: Surgery
O: Complete excision, recurrence, disease specific survival
S: Any study

SEARCH METHOD

Searches were conducted for primary studies on MedLine, Embase and for systematic reviews on The Cochrane Library including only studies published between 2000 and 2008

MedLine:
carcinoma AND colorectal surgery
T1 colorectal carcinoma AND colorectal neoplasms AND surgery
T1 colorectal carcinoma AND surgical resection AND recurrence
T1 colorectal carcinoma AND surgical resection AND long term survival
T1 colorectal carcinoma AND radical surgery AND recurrence
polypectomy AND colorectal neoplasms AND endoscopic treatment
polypectomy AND colorectal neoplasms AND criteria for endoscopic treatment
polypectomy AND colorectal neoplasms AND complete excision

Embase:
T1 carcinoma and colorectal and surgery
T1 colorectal carcinoma AND radical surgery AND recurrence

Cochrane Library:
We searched for Cochrane Reviews among the reviews published by the Colorectal Cancer Review Group

RESULTS

We found nine studies. Two were narrative reviews (1,2), two were retrospective case series (3,4), two were prospective prospective studies (5,6), two were a retrospective cohort studies (7,8) In addition, a US guideline was found [9]. No relevant Cochrane Reviews were retrieved

Narrative reviews

The narrative reviews summarise the current management strategies of early colorectal cancer – T1 and T2 lesions through a review of the literature (1, 2). Both reviews were published in 2008.

Mitchell 2008 (1) stated that treatment of malignant adenoma is highly dependent upon pathological assessment. Several risk factors should be taken into account by the clinician: level of invasion using Haggitt levels, resection margin, sessile *vs.* pedunculated polyps, and degree of differentiation according to histological grading (I-III). Low-risk malignant polyps should be treated by polypectomy and surveillance. Laparoscopic surgery and transanal endoscopic micro-surgery were suggested as alternatives to extensive surgery for T1 tumours .

Tytherleigh et al. 2008 (2) states that various surgical procedures are available for the management of early rectal cancer: standard polypectomy, advanced polypectomy or endoscopic mucosal resection, per anal excision or transanal endoscopic microsurgery and anterior resection. These surgical options need to be considered in relation to patient, clinical, endoscopic, radiological and, crucially, histological parameters. Low-risk ERC could be defined as completely excised Haggitt level 1–3 or Kikuchi Sm1 T1 adenocarcinoma with no evidence of poorly differentiated adenocarcinoma or lymphatic or vascular invasion. High-risk ERC could be commonly defined as one that has high histological grade, Sm3 and possibly Sm2 depth of invasion, together with the presence of lymphatic or vascular invasion.

Classical surgery affords the best chance of cure, but for low-risk early rectal cancer (ERC) local excision can match its outcomes while preserving rectal function. High-risk ERC can be treated by local excision, but oncological principles are compromised with correspondingly poor results.
Both papers conclude that following careful analysis of pathological risk factors, low risk cancers can be treated by endoscopic polypectomy or in the case of rectal cancer also by transanal excision. For high risk cancers, surgery should be considered against the morbidity and mortality associated with colonic resection.

Cohort studies

Endsreseth examined the long-term results of transanal excision compared with major surgery of T1 rectal cancer (5) and Chok examined factors that affect survival and recurrence in patients with T1 and T2 colorectal cancer treated with radical surgery (6).

Endsreseth (5) compared two techniques used for the treatment of rectal cancer patients in an observational prospective study. 256 patients had major surgery and 35 had transanal excision (in Norway the majority of patients have major surgery, which represents a selection bias). Selection bias is evident as the process of selection was based on surgeon and patient preference and resulted in different characteristics of the treatment groups. There were significant differences in age, distance from anal verge to the tumour, and tumour diameter in the two treatment groups, indicating that these variables were important in the selection of treatment modality. Preference is for major surgery for T1 rectal cancers in Norway. The male/female ratio was significantly lower in the transanal excision group. There were no differences in tumour size, location or differentiation between Stage I and III between the groups. Patients in the transanal excision group had higher rates of recurrence (12%) compared to 6% in the major surgery group.

Endsreseth concludes that transanal excision of early rectal cancer on a national basis is inferior to major surgery. The major problem with transanal excision for early rectal cancer is the inability to remove all of the malignancy.

Chok (6 made comparisons between patients with rectal cancer and those that had colon cancer, characteristics of T1 *versus* T2 tumours and patients with and without lymph node metastasis. No comparisons are made in this study with other surgical techniques. All patients had radical surgery.

5.6% of T1 patients had lymph node metastasis, the disease-free 5-year survival was 84.6% and the cancer specific 5 year survival 90.2%. 14.5% of T2 patients with lymph node metastasis, disease-free 5-year survival was 81.1% and cancer specific 5 year survival was 90.6%. Less extensive lymph node involvement appears to occur in early colorectal cancer. No differences were observed in survival between patients with T1 and T2 disease.

Chok concluded that the prognosis of patients depends on the presence of lymph node metastasis. Thus radical resection with meticulous examination of the resected specimen should be the optimal treatment option for patients with T1 and T2 colorectal cancers.

Bentrem 2005 (7) performed a retrospective cohort study comparing overall and local recurrence rate, overall 5 years survival and 5 years specific survival of two groups of patients with Ti rectal carcinoma treated by transanal excision(n.151) or radical surgery (n.168). Despite a similar risk profile in the 2 surgical groups, patients with T1 rectal cancer treated by local excision were observed to have a 3- to 5-fold higher risk of tumour recurrence compared with patients treated by radical surgery. Estimated disease-specific and overall survival rates were similar for RAD and TAE groups. Authors concluded that Local excision should be reserved for low-risk cancers in patients who will accept an increased risk of tumour recurrence, prolonged surveillance, and possible need for aggressive salvage surgery. Radical resection is the more definitive surgical treatment of T1 rectal cancers. Close postoperative cancer surveillance is inevitable in patients with T1 rectal cancer after local excision treatment.

Hahnloser 2005 (8) performed a retrospective cohort study comparing patients with t1 rectal cancer treated with local excision followe by radical surgery within 30 days (52 patients) with primary radical surgery (78 patients) or local excision alone (77patients). Radical surgery was performed after local excision because of a cancerous polyp (n = 42), positive margins (n=5), lymphovascular invasion (n=3), and T3-staged cancer (n=2). There were no significant difference in nodal involvement, local recurrence, distant metastasis, overall five and ten year survival. these result should be consdidered with caution because of the possibility of selection bias as there was no criteria for deciding whether to proceed with radical surgery, adjuvant therapy or close observation for patients that had had a previous local excision. Authors concluded that local excision of rectal tumours followed by radical surgery within 30 days in cancer patients does not compromise outcome compared with primary radical surgery. Even after radical surgery for superficial T1 rectal cancers, recurrence rates are not insignificant. Future improvements in preoperative staging may be helpful in selecting tumours for local excision only.

Case series
Wang 2005 (3) reviewed the features of T1 colorectal adenocarcinoma in patients who had curative resection and risk determination of lymph node metastasis. Prognostic factors were assessed to verify whether the risk of lymph node metastasis would influence the long-term prognosis. Histologic grade, lymphatic vessel invasion, inflammation around cancer and budding at the invasion front were risk factors for lymph node metastasis.

Floyd 2005 (4) reported the results of a case series of 53 patients with T1 rectal carcinoma treated by transanal endoscopic microsurgical resection (TEM). Recurrence was 7.5%. Authors concluded that TEM is a safe option for the excision of pT1 rectal cancers. With careful patient selection, full-thickness excision, and close surveillance, disease-free survival should be comparable to radical excision, with <10 percent of patients requiring salvage treatment for locally recurrent disease.

NCCN Guidelines (9)

Treatment for early stage colon cancer – T1, N0, M0 (stage I)
Biopsy and pathological assessment by polypectomy of the lesion are required for deciding appropriate treatment. If the malignant polyp is removed in one piece and it doesn't look aggressive, no further treatment is recommended. In the case of sessile polyps surgery should not be discounted. If the lesion is removed in fragments or tumour is found at the edge, then surgical resection of the colon is recommended.

Treatment for early stage rectal cancer – T1 N0, M0 (stage I)
Biopsy and pathological assessment by polypectomy of the lesion are required for deciding appropriate treatment. Treatment is based upon whether a pedunculated or sessile polyp is found and whether it was removed in one piece or in fragments.

Surgery is the first treatment recommended for rectal cancer by either abdominoperineal excision or by transanal excision (if less than 3 cm in size and no more than 8 cm from the anus). After surgery the tumour should be examined by a pathologist to ascertain if further abdominal surgery is required or recommended if the edges of the specimen contain cancer (transanal excision).

CONCLUSIONS

There is little comparative data in the literature examining the outcomes and risks of the various surgical techniques for T1 carcinomas, No RCTs have been conducted comparing local excision and radical resection.

The reported aims and methods described are different and generally not comparable across studies. In addition, patient inclusion criteria varied between the studies making comparisons difficult. Few studies on the management of colon cancer were found; conversely a number of studies dealing with the treatment of rectal cancer were retrieved.

An emerging conclusion from the literature was that the treatment of T1 rectal and colon cancer should be considered separately. Common to both was the concern surrounding local excision (due to high rate of recurrence, as this technique neglects risk of spread to regional lymph nodes) and the question of whether local excision could be offered to patients with results equivalent to surgical resection. It was noted by Bentrem that cancer in the rectum carries a higher risk of lymph node spread than proximally located cancers of the colon (15-25% vs. 3-8% respectively). Nevertheless, local excision of T1 rectal cancers has a significant risk of recurrence, and radical surgery should be advocated immediately after local excision in patients with adverse pathologic features. Given the benefits of lymphadenectomy with major surgery, the prevailing conclusion was that transanal excision of early rectal cancer should be recommended in patients at low risk of malignancy and recurrence. Each case should be reviewed carefully with particular emphasis placed on the pathological assessment to guide the management of T1 carcinomas, and the need for accuracy.

The majority of the studies suggest that improvements in pre-operative staging would be helpful when deciding whether local excision versus radical surgery is the optimal treatment strategy for the patient.

The NCCN Guidelines state that biopsy and pathological assessment is required when deciding appropriate treatment, supporting the overall conclusion from the assessed publications. These guidelines suggest that treatment is also dependent on whether a polyp is sessile or pedunculated. If the malignant polyp can be removed in one piece, with a negative resection margin and with favourable histological features, then endoscopic polypectomy is recommended. In all other cases, surgery is recommended.

For T1 rectal tumours that are node negative with manageable histology a transanal excision is recommended and for all other lesions surgery is recommended.
(LEVEL OF EVIDENCE III,V).

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8.2.2   Evidence tables

Author, publication year	Study objective	Study design Inclusion criteria	Results of search	Conclusions Level of evidence
Mitchell et al, 2008	To define factors involved in arriving at the correct management decision of either endoscopic polypectomy or colonic surgical resection.	Narrative Review Publications relating to diagnosis, pathology and management of malignant adenomas.	Treatment is dependent upon pathological assessment. Several risk factors should be taken into account by clinician: • Level of invasion using Haggitt levels. Level 4 invasion in pedunculated polyps and any malignancy in sessile polyps is classified as high risk • Resection margin: residual, recurrent disease and mortality more frequent in positive resections. 2mm margin considered necessary for complete removal. • Sessile *vs.* pedunculated polyps. Sessile polyps have been reported to have a worse clinical outcome than pedunculated polyps • Degree of differentiation according to histological grading (I-III). I-II grading is not considered high risk, III considered important risk-factor. • Lympho-vascular invasion was found not to be an important risk-factor for adverse outcome. <u>High risk factors</u>: Haggitt level 4, poor differentiation (grade III) and positive resection margin Other factors: • Avoid piecemeal fragmented removal of polyps due to the difficulty confirming adequate excision and sectioning	**V** After a review of 13 papers authors state that the treatment of choice for low-risk malignant polyps should be polypectomy and surveillance. Based on the results of Kryzer *et al*, 1992, the authors conclude that level 4 colorectal adenomas should be removed by surgical resection. 15 patients with Level 4 lesions, 3 had residual mucosal disease, 1 had lymph node metastases and 1 died from colorectal cancer *versus* 14 patients with lesions of levels 1-3 where none had residual tumour in the resection specimen or lymph node metastases. The state of the colonic mucosa should also be a factor in determining whether resection is appropriate – presence of multiple polyps in same segment as malignant polyp or strong family history of colorectal cancer. Risk: greater risk is involved with surgical resection than polypectomy : polypectomy : mortality rate is <0.1% and complication rate is 3%. Surgery: mortality rate is 0.8% - 3% to 9% in patients over 85 years. Authors suggest that laparoscopic surgery may offer reduced risk of mortality and morbidity. Transanal endoscopic microsurgery (TEM) may be an alternative to extensive surgery for T1 tumours. The risks of surgical resection should be balanced against the patient's polyp characteristics, residual disease and risk of metastases.

Narrative review: bibliographic search not specified in detail; Inclusion and exclusion criteria of primary studies not defined. Number of retrieved studies with the search, number of included and excluded studies not stated. Results of primary studies presented narratively.

Quality of reporting (QUOROM checklist)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE
	Date restriction	Not reported
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	publications relating to diagnosis, pathology and management of malignant adenomas.
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	Not reported
Study results	Descriptive data for each trial	Not reported
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Result presented narratively

Author, publication year	Study objective	Study design	Results	Conclusions Level of evidence

Tytherleigh et al. 2008.	To review the current management of early rectal cancer – T1 and T2 lesions through a review of the literature	Narrative revoiew 124 references	**Surgical options for early rectal cancer** Surgical options must encompass accurate histology, safe oncological surgical principles and the highest chance of cure. Any local treatment that destroys the tumour architecture or renders tumour tissue impossible to examine, such as electrocoagulation, endocavity radiation, and laser and cryotherapy, are not suitable for early rectal cancer (ERC).
			
			 Polypectomy
			
			 Surgical option Pathological stage
			 Standard polypectomy Pedunculated adenoma
			      ERC pT1 Haggitt level 1–3
			
			 Advanced polypectomy or endoscopic Flat and depressed adenomas <3cm
			 mucosal resection
			      ERC pT1 Sm1a and Sm1b without vessel invasion
			
			 Per anal excision or transanal Large adenomas
			 endoscopic microsurgery pT1 Sm1b and pT1 Sm2
			      pT1 Sm3 and possibly pT2 (in an
			 unfit patient)
			
			  Anterior resection pT1 Sm3 and possibly Sm2
			      Poor differentiation, vascular
			 invasion,
			      incomplete excision
			
			 Endoscopic mucosal resection uses the strip biopsy method, as described by Karita and colleagues. The lesion is marked with diathermy around its circumference and submucosal infiltration is performed. A barbed snare is used and the tumour removed in strips. Accurate histological examination is difficult and so this technique should be used only for tumours that are thought to be benign on preoperative staging.
			 Parks' per anal excision is possible for lesions within 6–10 cm of the anal margin.
				Level of evidence not assessable as the designd of included studies are not specified
				
				 Treatment selection for early rectal cancer The choice of surgical treatment relies on patient, clinical, endoscopic, radiological and, crucially, histological parameters. Often the best plan is made retrospectively once the tumour has been removed and the histological stage confirmed.
				
				 Treatment by local excision alone requires consideration of the chance of subsequent development of local recurrence or involved lymph nodes being left behind. If the tumour is associated with a high risk of lymph node metastases and recurrence following local excision, early classical surgery (within 30 days) does not compromise the oncological outcome compared with primary classical surgery. Treatment selection is based on the macroscopic classification of ERC according to Kudo1, the substaging of T1 adenocarcinoma in pedunculated polyps according to Haggitt and the substaging of T1 adenocarcinoma in sessile polyps according to Kikuchi. This allows the ERC to be classed as having a high or low risk of recurrence. It is difficult to be prescriptive regarding the precise surgical treatment options. ERC in an elderly, frail patient will often be treated differently to a similar lesion in a young fit patient, and treatment will also depend on whether the ERC is high or low risk

Author, publication year	Study objective	Study design	Results	Conclusions Level of evidence
			Minimally invasive transanal surgery is a further modification and enables local excision of tumours lying above the peritoneal reflection. Classical Surgery Anterior resection may be required for submucosal level (Sm) 3 and possibly Sm2 lesions, those with poor differentiation, lymphovascular invasion, a positive margin, or inadequate tissue for accurate histological assessment61 Abdominoperineal excision for an ERC should be unusual as there are many sphincter-preserving techniques that can be employed. Histopathological features of low- and high-risk early rectal cancer. Low-risk early rectal cancer Well or moderatelydifferentiated adenocarcinoma and mucinous adenocarcinoma No vascular or lymphatic invasion Kikuchi Sm1 and possibly Sm2 Haggitt 1–3 High-risk early rectal cancer Poorly differentiated adenocarcinoma and mucinous adenocarcinoma Signet ring and undifferentiated Vascular or lymphatic invasion Kikuchi Sm3 and possibly Sm2 Positive resection margin Relative factors Absence of lymphoid infiltration Tumour budding Poor demarcation at invasive front Poor differentiation at invasive front Cribriform-type structural atypia Position in distal third of rectum	Low-risk ERC completely excised Haggitt level 1–3 or Kikuchi Sm1 T1 adenocarcinoma with no evidence of poorly differentiated adenocarcinoma or lymphatic or vascular invasion. High-risk ERC commonly defined as one that has high histological grade, Sm3 and possibly Sm2 depth of invasion, together with the presence of lymphatic or vascular invasion Prognosis Disease recurrence after treatment of ERC depends on the histology and molecular biology of the cancer, lymph node involvement and type of surgery performed. Recurrence and survival rates are difficult to extrapolate from the published literature because of inconsistent definitions, the confusion of possible curative local excision for T1 Authors conclude that classical surgery affords the best chance of cure, but for low-risk ERC local excision can match its outcomes while preserving rectal function. High-risk ERC can be treated by local excision, but oncological principles are compromised with correspondingly poor results.

Narrative review: bibliographic search specified (database and years); Inclusion and exclusion criteria of primary studies not defined. Number of retrieved studies with the search, number of included and excluded studies not stated. Results of primary studies presented narratively. Study designs not discussed.

Quality of reporting (QUOROM checklist)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE , ,COCHRANE DATABASES'. The bibliographies of extracted articles were further cross-referenced
	Date restriction	from1995 to 2006
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	Not reported
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	Not reported
Study results	Descriptive data for each trial	Not reported
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Result presented narratively

Author, publication year	Study objective	Study design	Participants	Outcomes	Results	Conclusions Level of evidence
Endreseth et al. 2005.	To examine long-term results of transanal excision compared with major surgery of T1 rectal cancer	A prospective national cohort study in Norway of 291 patients with a T1M0 tumour within 15cm from the anal verge treated by anterior resection, abdominoperineal resection, Hartmann's procedure, or transanal excision 256=major surgery 35=transanal excision	291 patients with T1M0 tumours treated by anterior resection (AR), abdominoperineal resection (APR), Hartmanns procedure, or transanal excision.. None of the patients received neoadjuvant therapy, but four patients in the major surgery group had postoperative radiotherapy because of intraoperative perforation of the bowel wall.	Local recurrence, survival Distant metastases	5yr year rate of local recurrence transanal group 12 % (95 % CI 0–24) major surgery 6 % (95 % CI, 2–10) (P = 0.01). Distant metastasis transanal group 0 % major surgery 7 % (95 % CI, 4–11) in (P = 0.52). Overall 5yr-year survival transanal excision group: 70 % (95 % CI, 52–88) major surgery group: 80 % (95 % CI, 74–85) (P = 0.04). Disease-free survival transanal excision group: 64 % (95 %CI, 46– 82) major surgery group :77 % (95 % CI, 71–83) (P =0.01) Treatment modality did not significant influence on survival, whereas gender and age did. Postoperative mortality 2.3% major surgery 2.9% transanal excision	**III** Higher rates of local recurrence and inferior overall and disease-free survival were seen after transanal excision compared with major surgery The results suggest that transanal excision of early rectal cancer on a national basis is inferior to major surgery. In the present study the main problem of transanal excision of early rectal cancer was the inability to remove the entire primary tumour. Eleven percent of the patients with T1M0 tumours who underwent major surgery had glandular involvement, and, based on this finding, it may be assumed that local treatment of early rectal cancer leaves metastatic lymph nodes in 11 percent of the cases. Patients treated with transanal excision had a significantly higher rate of local recurrence compared with patients who underwent major surgery. To achieve acceptable results and make locoregional treatment of early rectal cancer a credible alternative to major surgery, improved surgical techniques for local treatment procedures and the use of neoadjuvant therapy have to be implemented.

Quality assessment: selection bias evident as the process of selection based on surgeon and patient preference resulted in different characteristics of the treatment groups. There were significant differences in age, distance from anal verge to the tumour, and tumour diameter in the two treatment groups, indicating that these variables were important in the selection of treatment modality. Preference for major surgery for T1 rectal cancers in Norway. The male/female ratio was significantly lower in the transanal excision group.

Author, publication year	Study objective	Study design	Participants	Results	Conclusions Level of evidence
Chok + Law. 2007.	Aims of the present study were to analyse the characteristics of T1 and T2 colorectal cancer and to determine the risk factors that might affect survival and recurrence in patients with T1 and T2 colorectal cancer treated with radical surgery	Prospective study	265 patients (144 men) with the median age of 71 years (range: 33–93 years) with T1 or T2 colorectal cancers who underwent radical surgery resection in the Hong Kong	72 patients: T1 cancer - 44 rectal - 28 colon LN metastasis: 5.6% Disease-free 5-yr survival: 84.6% Cancer specific 5yr survival: 90.2% 193 patients: T2 cancer - 120 rectal - 73 colon Disease-free 5-yr survival: 81.1% Cancer specific 5yr survival: 90.6% Size of tumour Significantly smaller in patients with T1 cancer (24.6mm versus 35.9mm). Lymph node metastasis Higher in patients with T2 cancer compared to T1 patients. 5.6%= T1 16%=T2 Lymphovascular permeation Higher in T2 patients than T1 (16 versus 2 respectively).	III The presence of lymphovascular permeation was the only significant predictive factor for lymph node metastasis. The incidence of lymphovascular invasion was only 6.8%, 50% of those with lymphovascular invasion were found to have lymph node metastasis. The site of the tumour had no impact on the occurrence of lymph node metastasis There were no differences in the survival between those with T1 disease and those with T2 disease. The presence of lymph node metastasis was the only significant independent factor predicting poor survival. Other adverse pathologial factors, such as differentiation or lymphovascular permeation or mucinous tumours were not associated with poorer survival. Radical resection is definitely indicated, especially if lymphovascular permeation is present. The prognosis of patients depends on the presence of lymph node metastasis. Thus radical resection with meticulous examination of the resected specimen should be the optimal treatment option for patients with T1 and T2 colorectal cancers.

Quality assessment: Representative cohort of people at average risk of colorectal cancer included in the study. Avoidance of selection bias, all patients had radical surgery in both cohorts. Gender, age, size of tumour and incidence of lymph node metastasis were comparable in the two groups. Both groups were selected from the same database from the same medical centre. Inclusion and exclusion criteria adequately described. Follow-up of cohort: calculated 5 year survival, however, median follow-up was 43.8 months. Out of 256 patients, 10 died in the post-operative period (these were excluded from the statistical analysis). Thus, follow-up of patients not complete. No description provided of the exact follow times for each patient.

Author, publication year	Study objective	Study design	Participants	Results	Conclusions Level of evidence
Wang et al. 2005	Review of the features of T1 colorectal adenocarcinoma and the risk determination of lymph node metastasis	Retrospective case series of patients undergoing curative resection of T1 colorectal adenocarcinoma The associations between lymph node metastasis and clinicopathologic variables were evaluated univariately using the chi-squared test for qualitative and ordinal discontinuous variables. Fisher's exact test was used if one of the cells had expected counts less than five. For continuous data that were normally distributed, a Student's t-test was used. Variables that were found to be significant in the univariate analysis were further studied multivariately using logistic regression China	159 patients were included. Sixteen patients (10.1 percent) had lymph node metastasis	The risk of lymph node metastasis included histologic grade ($P = 0.005$), lymphatic vessel invasion ($P = 0.023$), inflammation around cancer ($P = 0.049$), and budding at the invasive front of tumour ($P = 0.022$). Age ($P = 0.001$) and number of total sampling lymph nodes ($P < 0.0001$) were found to be the factors influencing the overall survival.	**V** Histologic grade, lymphatic vessels invasion, inflammation around cancer, and budding at the invasive front of tumour were risk factors of lymph node metastasis, However, only age and number of total sampling lymph nodes could be identified to influence the prognosis in the same group of patients. The risk factors of lymph node metastasis could not predict the overall survival. Therefore, when defining the treatment strategy for patients with T1 colorectal carcinoma, it is important to consider both the risk of lymph node metastasis and long-term prognosis.

Author, publication year	Study objective	Study design	Participants	Follow up	Results	Conclusions Level of evidence
Floyd et al. 2005	To show that transanal endoscopic microsurgical treatment of pT1 rectal cancers is safe and achieves low local recurrence and high survival rates.	Retrospective case series of all pT1 rectal cancers treated by a single surgeon (TS) using transanal endoscopic microsurgery. Patient age, gender, tumour distance from the anal verge, lesion size, operative time, blood loss, complications, recurrence, and survival rates were prospectively recorded.	53 patients (average age, 65.6 (range, 31–89) years) were studied. Forty-nine % were male. Average tumour distance from the anal verge was 7 (range, 0–13) cm; average size was 2.4 (range, 1–10) cm.	Mean follow-up was 2.84 years. Fifty-one percent had longer than two-year follow-up.	Radiation and/or chemotherapy were not administered. Recurrences :7.5 % occurring at 9 months, 15 months, 16 months, and 11 years. Two were treated with abdominoperineal resection, one with low anterior resection, and one with fulguration alone. 16 had pT1 lesions removed piecemeal by colonoscopy and had no histologic evidence of residual tumour after TEM. None of these patients developed recurrence.. If excluded, recurrence was 11 % (4/37). There have been no cancer-related deaths.	V Authors conclude that TEM is a safe option for the excision of pT1 rectal cancers. With careful patient selection, full-thickness excision, and close surveillance, disease-free survival should be comparable to radical excision, with <10 percent of patients requiring salvage treatment for locally recurrent disease.

Author, publication year	Study objective	Study design	Participants	Interventions	Follow up	Results	Conclusions Level of evidence
Bentrem et al. 2005	Compare the risk of tumour recurrence observed in a local excision cohort versus a radical surgery cohort for T1 cancers	Retrospective cohort study	319 patients who underwent surgery for T1 adenomas of the rectum (0-15cm from anal verge)	Transanal excision (TAE): n.151 radical surgery (RAD): n: 168	5 years	5 year recurrence rate for all patients: 12% 5 year overall recurrence rate TAE group:23% (95% CI, 13–29%) RAD group 6% (95% CI, 2–9%) (P <0.001) 5 year local recurrence rate TAE group 15% RAD group:3% (p = 0.0001) Estimated disease-specific and overall survival rates were similar for RAD and TAE groups. Estimated 5yr disease-specific survival rate TAE 93% RAD: 97% (P=0.05) Estimated 5yr overall survival rate TAE: 89% RAD:93% (P=0.17) Of the patients who recurred after local excision, 16 of 19 patients with local recurrence underwent complete resection, including 3 of 5 patients who also had a distant site of recurrent disease.	III Despite a similar risk profile in the 2 surgical groups, patients with T1 rectal cancer treated by local excision were observed to have a 3- to 5-fold higher risk of tumour recurrence compared with patients treated by radical surgery. Local excision should be reserved for low-risk cancers in patients who will accept an increased risk of tumour recurrence, prolonged surveillance, and possible need for aggressive salvage surgery. Radical resection is the more definitive surgical treatment of T1 rectal cancers.

Quality assessment: selection bias: there is a small pitfall in that patients selected for local excision were slightly older than those selected for radical surgery and their tumours slightly smaller. Thus, there was a preference for local excision in older patients and low-lying tumours versus radical surgery which favoured larger and higher-lying cancers. In addition, patients that had radical surgery had adjuvant chemotherapy whereas the local excision cohort did not receive chemotherapy as part of their initial treatment; heterogeneous treatment received by patients in the radical surgery cohort. Unclear if follow-up time and size of cohort is sufficient to analyse recurrence. Medical records were accessed for both cohorts using the same method.

Author, publication year	Study objective	Study design	Participants	Interventions	Results	Conclusions Level of evidence
Hahnloser et al. 2005	To determine the frequency and outcome when the decision was made to proceed with radical resection within 30 days after local excision for rectal adenocarcinoma. These results were compared with those for patients who underwent either primary radical resection or only local excision in a stage-matched fashion.	Retrospective cohort study	202 patients with T1N0-1 cancers	Local excision followed by radical surgery within 30 days (n, 52) primary radical surgery (n = 78) local excision alone (n = 77). Radical surgery was performed after local excision because of a cancerous polyp (n = 42), positive margins (5), lymphovascular invasion (3), and T3-staged cancer (2).	Nodal involvement Local excision followed by radical surgery :21% Primary radical surgery: 15% ($P = 0.08$). Local recurrence: Local excision followed by radical surgery :3% Primary radical surgery: 5% Local excision alone: 8% Distant metastasis: Local excision followed by radical surgery :11% Primary radical surgery: 12% Local excision alone: 13% Overall five years survival Local excision followed by radical surgery :79% Primary radical surgery: 91% Local excision alone: 73% (P:NS) Overall ten years survival Local excision followed by radical surgery :65% Primary radical surgery: 78% Local excision alone: 45% (P:NS) Overall survival was shorter for the local excision-only group ($P <0.001$), but cancer-free survival was comparable ($P = 0.4$). This difference most likely is a result of the increased age at the time of surgery in the local excision-only group	**III** Local excision of rectal tumours followed by radical surgery within 30 days in cancer patients does not compromise outcome compared with primary radical surgery. Even after radical surgery for superficial T1 rectal cancers, recurrence rates are not insignificant. Future improvements in preoperative staging may be helpful in selecting tumours for local excision only. Local excison criteria: proximal margin of lesion <10mm from anal verge, diameter <3 – 4 mm, circumferential involvement <33% of rectum. Whole-tumour histologic evaluation after en bloc resection is the best way to evaulate polyp maignancy to indicate the need for surgery and adjuvant therapies. Pathologic features, such as poor differentiation, lymphovascular or perineural infiltration, and mucin production have been associated with an increased local recurrence rate after transanal excision and may indicate the need for further treatment. However, the final pathologic TNM stage remains the most powerful predictor of postoperative outcome, but preoperative identification of patients with disease limited to the rectal wall (T1/2N0M0) is difficult.

Quality assessment: Selection and definition of controls defined. Clinical records were accessed from a single medical centre over a set period of time for both controls and cases. Selection bias as there was no criteria for deciding whether to proceed with radical surgery, adjuvant therapy or close observation for patients that had had a previous local excision. Outcomes of review defined. Inclusion and exclusion criteria for patients specified. Non response rate not mentioned.

Author, publication year	Guidelines
Colon and Rectal Cancer Treatment Guidelines for Patients American Cancer Society and National Comprehensive Cancer Network 2007	<u>Treatment for early stage colon cancer – T1, N0, M0 (stage I)</u> *Question 2* Biopsy and pathological assessment by polypectomy of the lesion are required for deciding appropriate treatment. If the malignant polyp was removed in one piece and it doesn't look aggressive, no further treatment is recommended. In the case of sessile polyps surgery should not be discounted. If the lesion is removed in fragments or tumour is found at the edge then surgical resection of the colon is recommended. <u>Treatment for early stage rectal cancer – T1 N0, M0 (stage I)</u> *Question 2* Biopsy and pathological assessment by polypectomy of the lesion are required for deciding appropriate treatment. Treatment is based upon whether a pedunculated or sessile polyp is found and whether it was removed in one piece or in fragments. If a pedunculated polyp is removed in one piece with no tumour found at the edge and is not aggressive then no further treatment is recommended. For sessile polyps, surgery should not be discounted even if the polyp was removed in one piece, there was no tumour at the edge and it is not aggressive. If a pedunculated or sessile polyp is removed in fragments or if it's unknown if the tumour has been completely removed then surgery is recommended. <u>Surgery</u> Surgery is the first treatment recommended by either abdominoperineal excision or by transanal excision (if less than 3cm in size and no more than 8cm from the anus). After surgery the tumour should be examined by a pathologist to ascertain if further abdominal surgery is required, recommended if the edges of the specimen contain cancer (transanal excision). <u>Treatment for advanced stage of colorectal cancer (Stage IV)</u> *Question 3* There are several initial treatment options if the cancer has grown through the muscle layer (T3) or there are enlarged lymph nodes on MRI or ultrasound (N1-2). One option is radiation therapy first, either with continuous 5-FU or with a bolus infusion of 5-FU combined with leucovorin, or with capecitabine. Of these chemotherapy plus radiation options, continuous 5-FU is preferred if the cancer has spread to the lymph nodes. This initial treatment is followed by a transabdominal resection, with more chemotherapy after surgery. Or. A transabdominal resection may be done first. Further treatment depends on the pathologist's findings. If it turns out that the tumour has not invaded through the muscle layer or spread to lymph nodes, no further treatment is recommended. If the tumour has spread through the muscle layer or involves lymph nodes, chemo and radiation treatment is delivered in 3 phases, as described in the Decision Tree. If the cancer has invaded through the rectal wall into nearby tissues or organs and cannot be removed, the NCCN recommends that treatment begin with radiation therapy to the pelvis combined with continuous 5-FU, or a single injection of 5-FU with leucovorin, or capecitabine pills. Afterward, the tumour should be removed by an abdominal operation. If possible. Following surgery 5-FU with or without leucovorin should be given. FOLFOX or capecitabine may also be considered. After treatment patient should see their doctor for a check up every 3 to 6 months for 2 years, then every 6 months for at least 5 years. CEA blood tests should be done along with the check up for tumours that are T2 or greater but only in patients who are well enough to consider further therapy if the cancer recurs. A CT scan of the chest, abdomen and pelvis may be done yearly for 3 years in patients considered to be at high risk for recurrence. Colonoscopy should be done 1 year after surgery. If polyps are found, it should be repeated in 1 year. If the colonoscopy is normal, it can be repeated in 3 years and then every 5 years. If colonoscopy could not be done before surgery, then the first one should be done with 3 to 6 months after surgery. If the tumour was removed through the abdomen, a proctoscopy may be recommended every 6 months for 5 years. PET scans are not recommended for routine

Author, publication year	Guidelines
	follow up.

Quality assessment: These are treatment guidelines for patients based on the NCCN Clinical Practice Guidelines in Oncology for Colon Cancer and Rectal Cancer V.1.2008.

NCCN Colon and Rectal Cancer Panel members are listed with clinical specialisation. NCCN uses its own internal categories of evidence and consensus to grade its recommendations. A complete list of references is provided. The inclusion criteria for primary studies are not stated. There is uniform NCCN consensus on all recommendations, however, the method used to analyse the evidence and how consensus is reached is not described. The search strategy is not described.

8.3 Treatment of rectal adenoma and T1 cancer by transanal endoscopic surgery

8.3.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 3

Treatment of rectal adenoma and T1 cancer by transanal endoscopic microsurgery (TEM)

PICOS

P: Patients with rectal adenoma and T1 rectal cancer
I: Transanal endoscopic microsurgery (TEM)
C: Existing techniques such as anterior resections and abdominoperineal resections or local excisions.
O: Complete excision, recurrence, disease specific survival
S: Any study design

SEARCH METHOD

Searches were conducted for primary studies on MedLine, Embase and for systematic reviews on The Cochrane Library including only studies published between 2000 and 2008.

MedLine and Embase:
polypectomy AND endoscopy AND management AND small polyps
polypectomy AND colorectal neoplasms AND endoscopic treatment
polypectomy AND rectal polyps AND criteria for endoscopic treatment
polypectomy AND colorectal neoplasms AND complete excision
polypectomy AND colorectal polyps AND surgical removal
polypectomy AND colorectal polyps AND laparoscopic removal
[Mesh] colorectal neoplasms AND colorectal surgery AND recurrence
[Mesh] endoscopy, gastrointestinal AND colonic polyps AND safety
pedunculated adenomas AND management
colonoscopy AND snare electrocoagulation
(Mesh) rectal neoplasms AND (TEM OR TEMS OR transanal endoscopic microsurgery OR endoscopic surgery OR microsurgery)

Cochrane Library:
We searched for Cochrane Reviews among the reviews published by the Colorectal Cancer Review Group.

We also looked at the references of retrieved articles to find other relevant paper.

RESULTS

Two systematic reviews on transanal endoscopic microsurgery were located (1,2).

2 case series (3,4) and 1 RCT published after the most recent update search of the systematic review were located. (5)

Middletone 2005 (1) performed a systematic review of good methodological quality to review the evidence relating to the safety and efficacy of TEM compared with existing techniques such as anterior resections and abdominoperineal resections or local excisions. A comprehensive bibliographic search was performed on several databases from 1980 to august 2002. 1 RCT, 2 non randomised comparative studies and 55 case series have been included. The RCT (Winde 1997) compare TEM vs local excision for adenoma (n= 188) and TEM vs AR for T1 carcinoma (n= 53).

Safety and efficacy of adenomas.
In the RCT, no difference could be detected in the rate of early complications between TEM and local excision. TEM resulted in less local recurrence than local excision .Median local recurrence in case series was 5%. Results of the non randomised study must be interpreted with caution because of risk of selection bias and unbalance of group: surgical decision was made according to the stage and size of adenoma; TEM: n= 80; RR: n=16. Tumours undergoing radical resection were likely to be more advanced than those selected for TEM, which would tend to bias the results in favour of TEM.

Safety and efficacy of carcinomas.
In the RCT, no difference could be detected in the rate of complications between TEM and anterior resection. No differences in survival or local recurrence rate between TEM and anterior resection could be detected in either the RCT or the non randomised study. In the case series, the median local recurrence rate for TEM was 8.4. Authors concluded that the evidence regarding TEM is very limited, being largely based on a single relatively small RCT. However, TEM does appear to result in fewer recurrences than those with direct local excision in adenomas and thus may be a useful procedure for several small niches of patient types—*e.g.,* for large benign lesions of the middle to upper third of the rectum, for T1 low-risk rectal cancers, and for palliative, not curative, use in more advanced tumours. Although no differences between TEM and radical resection could be detected for most outcomes, decreased pain and the likely shorter hospital stay will be attractive to patients and clinicians.

Suppiah 2007 (2) performed a systematic review to assess the effectiveness and safety of TEM compared to anterior resection for cancer of the rectum. A bibliographic search was performed on the medline database up to June 2006. 2 RCTs, 3 comparative non randomised trials and 28 case series were included. One of the included RCT is included also in the review by Middleton 2005 (Winde 1997), the other is the results at three year follow up of the Lezoche trial [22]. One of the comparative non randomised trial is included also in the review by Middleton. Both RCTs found no difference in survival rate (3 and 5 year follow up) and local recurrence. In both trials TEM is associated with lower operating time, blood loss and length of hospital stay. In the comparative non randomised studies there were no differences in 5 years survival, less complications, transfusion and length of hospital stay with TEM. Local recurrence was higher with TEM for high risk lesions and T2 cancer. Author concluded that the risk of disease recurrence and quality of life and non cancer related death should be balanced when deciding between radical surgery and local excision in rectal caner, particularly in elderly patients. Definite conclusions could not be drawn based on the existing evidence. A large randomised controlled trial comparing TEM + ∕ - neo-adjuvant therapy against RR in selected patients and tumour types should be undertaken. Unlike previous trials, the outcome should not just emphasis cancer recurrence rates but should also include immediate and long-term morbidity, gastrointestinal function and quality of life.

Lezoche 2008 (5) performed a randomised controlled trial on 75 patients with T2 N0 rectal cancer comparing local excision by TEM (n= 35) with laparoscopic resection by total mesorectal excision or abdominoperineal resection (n= 35). The patients undergoing TEM had significantly less operative time, blood loss, analgesic consumption and hospital stay than the patients undergoing LR (p<0.001). There were no significant difference in postoperative complication, local recurrence, distant metastases and survival at five year follow up.

Ganai 2006 (3) reported the results of a case series of 139 patients with preoperative diagnosis of rectal adenoma in 109 (76%) cases, adenocarcinoma in 28 (19%), carcinoid tumour in 4 (3%), and other in 3 (2%) treated by transanal endoscopic microsurgery (TEM). Complication occurred in 10% of cases and recurrence in 15%. Five-year neoplastic recurrence probabilities were 11% for benign adenomas, 35% for adenomas with HGD, and 20% for cancers. On multivariate analysis, independent predictors of recurrence were lesion size and the presence of HGD within adenomas (P <0.05). Authors concluded that close endoscopic follow-up is warranted after TEM for both benign and malignant disease, with special attention to lesions with HGD. TEM can be performed safely for early rectal cancer with careful patient selection.

Zacharakis 2007 (4) reported the results of a case series of 76 patients with preoperative histologic diagnosis of rectal benign adenoma [54] and adenocarcinoma [22] treated by transanal endoscopic microsurgery (TEM). In the Subgroup of benign lesions clear resection margins were found in 95.7%; complications in 2% (1 case of perforation). The recurrence rate was 6.3%. Authors concluded that TEMS is a safe and feasible technique with low incomplete excision rates and may be the preferred method in patients with benign tumours of the mid- and upper rectum. Its role in the management of malignant rectal tumours should be limited to selected patients with T1 tumours, although its role in combination with adjuvant or neoadjuvant chemoradiotherapy warrants further investigation.

CONCLUSIONS

Only two RCTs and three comparative non randomised trials have been retrieved. One RCT and one comparative non randomised study compared TEM with local excision for adenoma. Two RTCs and three comparative non randomised trials compared TEM with surgery for carcinoma. The first RCT (Wind 1996) compares TEM with anterior resection for T1 carcinoma, the second RCT (Lezoche 2005, 2008) compares TEM with laparoscopic resection by total mesorectal excision or abdominoperineal resection for T2 N0 carcinoma. All the other retrieved studies are case series reporting recurrence and complication rates of TEM in patients with rectal adenoma or T1-T2 carcinoma.

Adenoma:

Based on the only RCT for adenoma no difference could be detected in the rate of early complications between TEM and local excision. TEM resulted in less local recurrence than local excision. In the case series the median recurrence rate for TEM was 5% (range 0 to 15.8%). The evidence regarding TEM is very limited, being largely based on a single relatively small RCT. However, TEM does appear to result in fewer recurrences than those with direct local excision in adenomas and thus may be a useful procedure for several small niches of patient types, e.g., for large benign lesions of the middle to upper third of the rectum (LEVEL OF EVIDENCE: II).

Carcinoma:

For carcinoma no difference could be detected in the rate of complications between TEM and radical surgery. No differences in survival or local recurrence rate between TEM and anterior resection could be detected in either the RCT or the non randomised trials. The patients undergoing TEM had significantly less operative time, blood loss, analgesic consumption and hospital stay than the patients undergoing curative surgery (p<0.001). In the case series, the median local recurrence rate for TEM was 8.4 %(range 0 % to 50 %). TEM is considered a promising procedure for treating T1 and T2 carcinoma of the rectum with adequate preoperative neoadjuvant therapy but it should be considered that the reported studies may have been of insufficient power to detect significant differences in mortality and recurrence (LEVEL OF EVIDENCE I).

REFERENCES

1. Middleton PF, Sutherland LM & Maddern GJ (2005), Transanal endoscopic microsurgery: a systematic review, *Dis.Colon Rectum*, vol. 48, no. 2, pp. 270-284.

2. Suppiah A, Maslekar S, Alabi A, Hartley JE & Monson JR (2008), Transanal endoscopic microsurgery in early rectal cancer: time for a trial?, *Colorectal Dis.*, vol. 10, no. 4, pp. 314-327.

3. Ganai S, Kanumuri P, Rao RS & Alexander AI (2006), Local recurrence after transanal endoscopic microsurgery for rectal polyps and early cancers, *Ann.Surg.Oncol*, vol. 13, no. 4, pp. 547-556.

4. Zacharakis E, Freilich S, Rekhraj S, Athanasiou T, Paraskeva P, Ziprin P & Darzi A (2007), Transanal endoscopic microsurgery for rectal tumours: the St. Mary's experience, *Am J Surg.*, vol. 194, no. 5, pp. 694-698.

5. Lezoche G, Baldarelli M, Guerrieri M, Paganini AM, De SA, Bartolacci S & Lezoche E (2008), A prospective randomised study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy, *Surg.Endosc.*, vol. 22, no. 2, pp. 352-358.

8.3.2   Evidence tables

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Ganai 2006	To examine the outcomes of local excision with transanal endoscopic microsurgery (TEM) in the management of benign and early malignant rectal lesions. retrospective case series USA	139 patients with preoperative diagnosis of adenoma in 109 (76%) cases, adenocarcinoma in 28 (19%), carcinoid tumour in 4 (3%), and other in 3 (2%).	The TEM operative technique was conducted with patients under general anesthesia by using a 20-cm-long operating rectoscope Carbon dioxide insufflation was used. Lesions were excised circumferentially with at least 10-mm macroscopic margins via either partial-thickness excision (mucosectomy) or full-thickness excision to perirectal fat. The defects were closed transversely by using absorbable suture secured by a clip.	Completion of excision Recurrence rate Predictors of recurrence on multivariate analysis Complication Conversion	5 years	Full-thickness excision was completed in 94 (65%) cases. Mucosectomy was performed in 35 (24%) cases, Recurrence: 15% Five-year neoplastic recurrence probabilities were 11% for benign adenomas, 35% for adenomas with HGD,and 20% for cancers. On multivariate analysis, independent predictors of recurrence were lesion size and the presence of HGD within adenomas (P <.05). Complication: 10%	**V** Close endoscopic follow-up is warranted after TEM for both benign and malignant disease, with special attention to lesions with HGD.TEMcan be performed safely for early rectal cancer with careful patient selection.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Zacharakis 2007	To evaluate its feasibility, morbidity, and recurrence rates of Transanal endoscopic microsurgery (TEMS) in patients with carcinoma and large adenomas of the rectum retrospective case series UK	76 patients with preoperative histologic diagnosis of rectal benign adenoma (54) and adenocarcinoma (22). Criteria for patient selection were mobile tumours <5cm in size, occupying <50% of the rectal circumference, and located 4 to 18 cm from the anal verge.	The TEMS operative technique was performed using a 40-mm rectoscope with patients under general anesthesia and positioned so that the lesion was orientated at the inferior aspect of the operative field. Carbon dioxide insufflation was used for the pneumorectum. Lesions were excised circumferentially with at least 10-mm macroscopic margins by way of either full or partial thickness excision when the lesions were located in the intraperitoneal rectum..	Completion of excision Recurrence rate Incomplete excision Complication	Mean 37 months	Clear resection margins: 95.9% Complication: 18.4% **Subgroup of benign lesions:** Clear resection margins: 95.7% Complication: 2% (perforation) Recurrence: 6.3%	**V** TEMS is a safe and feasible technique with low incomplete excision rates and may be the preferred method in patients with benign tumours of the mid- and upper rectum. Its role in the management of malignant rectal tumours should be limited to selected patients with T1 tumours, although its role in combination with adjuvant or neoadjuvant chemoradiotherapy warrants further investigation.

Author, publication year	Study objective Study Design	Bibliographic search	Inclusion criteria	Outcomes	Results	Level of evidence Conclusions
Middleton 2005	To systematically review the evidence relating to the safety and efficacy of TEM, compared with existing techniques such as anterior resections and abdominoperineal resections or local excisions. systematic review Australia	Medline, Embase, Science Citation Inx, Current contents, Cochrane Library, NHS CRD, (National Research Register, www.clinicaltrials.gov, 1980-august 2002.	RCT, controlled non randomised studies , case series comparing for malignant tumours TEM with anterior resections; abdomino-perineal resections, posterior proctectomies (PP), or local excisions. For benign tumours the comparative interventions were AR or LE.	Safety: perioperative mortality, perioperative morbidity or complications, postoperative mortality, and postoperative morbidity or complications, Postoperative histopathology Pain, Effectiveness, : operating time, rate of conversion to open or other procedures, complete or incomplete resection, need for subsequent radical rectal excision, length of hospital stay, readmission rate, reoperation rate, and anorectal function Patient satisfaction and quality of life outcomes Survival recurrence	1 RCT :TEM vs AR for T1 carcinoma (n.53) and vs local excision for adenomas (n.188) 2 controlled non randomised: TEM vs AR for adenoma (n.96); TEM vs RR for carcinoma (n. 80 low risk; n.23 high risk) 55 case series Safety and efficacy of adenomas. In the RCT, no difference could be detected in the rate of early complications between TEM and local excision: RR 0.61; (95 %CI, 0.29–1.29). TEM resulted in less local recurrence than local excision RR, 0.28; 95 %CI, 0.12–0.66). The 6 percent rate of local recurrence for TEM in this trial is consistent with the rates found in case series of TEM (median, 5 percent range 0 to 15.8 %). Results of the non randomised study must be interpreted with caution because of risk of selection bias and unbalance of group: surgical decision was made according to the stage and size of adenoma; TEM: n.80; RR: n.16. Tumours undergoing radical resection were likely to be more advanced than those selected for TEM, which would tend to bias the results in favour of TEM. Safety and efficacy of carcinomas. In the RCT , no difference could be detected in the rate of complications between TEM and anterior resection (RR, 0.56; 95 %CI, 0.22–1.42). No differences in survival or local recurrence rate between TEM and anterior resection could be detected in either the RCT (HR,1.02 for survival) or the comparative non randomised	**II** The evidence regarding TEM is very limited, being largely based on a single relatively small RCT. However, TEM does appear to result in fewer recurrences than those with direct local excision in adenomas and thus may be a useful procedure for several small niches of patient types—*e.g.,* for large benign lesions of the middle to upper third of the rectum, for T1 low-risk rectal cancers, and for palliative, not curative, use in more advanced tumours. TEM should be regarded as a niche procedure suitable for treating only a small percentage of rectal tumours. Although it is not clear whether TEM is safer than LE, both procedures have relatively low complication rates and TEM does appear to result in less local recurrences than LE. Although no differences between TEM and radical

Author, publication year	Study objective Study Design	Bibliographic search	Inclusion criteria	Outcomes	Results	Level of evidence Conclusions
					trial. Operating time and hospital stay were significantly less for TEM patients. In the non randomised trial, there were significantly less complications in the TEM/LE group (1/46) than in the radical resection group (5/34) with low-risk carcinomas ($P = 0.04$) no difference was detected between the groups with high-risk carcinomas. In the case series, the median local recurrence rate for TEM was 8.4 %(range 0 % to 50 %	resection could be detected for most outcomes, decreased pain and the likely shorter hospital stay will be attractive to patients and clinicians.

Quality assessment: bibliographic search: databases reported and key words reported. No language restriction. Studies assessed for inclusion and data extracted by two independent reviewers. Inclusion criteria clearly stated. Methodological quality of primary studies assessed using validated checklist. Number of included and excluded studies reported.

Author, publication year	Study objective	Study Design	Inclusion criteria	Outcomes	Results	Level of evidence Conclusions
Suppiah 2007	To evaluate the role of TEM in rectal carcinoma with emphasis on cancer outcomes, postoperative gastro-intestinal function and quality of life. UK	Systematic review	Comparative and individual studies publishing results of TEM in adenoma and carcinoma were reviewed. All studies had to report at least one of the following primary outcome measures: local recurrence rate, systemic recurrence, overall ∕ disease-free survival or probability of survival.	Safety: perioperative mortality, perioperative morbidity or complications, postoperative mortality, and postoperative morbidity or complications, Postoperative histopathology Effectiveness: operating time, rate of conversion to open or other procedures, complete or incomplete resection, need for subsequent radical rectal excision, length of hospital stay, readmission rate, reoperation rate, and anorectal function Patient satisfaction and quality of life outcomes Survival recurrence	2 RCTs (1 also included in Middleton (Winde 1997), 1 is the three year follow up results of the same trial we included in our review with 5 year follow up (Lezoche 2005) 3 retrospective case comparisons (1 also included in Middleton 2005) 28 case series Safety and efficacy of carcinomas. **Winde RCT**: TEM vs radical resection for T1 carcinoma: no difference in local recurrence and five year survival. TEM had less complications, 20.8% vs 34.5% (P: NS) , decreased mean operative time (103 min vs 149 min; P <0.05), decreased blood loss (143 ml vs 745 ml; P <0.001) decreased daily analgesia requirement (P <0.0001) and LOS (5.7 days vs 15.4 days; P <0.001) **Lezoche RCT**: TEM vs laparoscopi resection for T2 N0 carcinoma: no difference in recurrence and survival; TEM associated with decrease operating time (95 min vs 170 min; P <0.001), decreased blood loss (50 ml vs 200 ml; P <0.001) analgesic use (2% vs 20%; P <0.001) and LOS (4.5 days vs 7.5 days; P <0.001). **3 comparative non randomised**: TEM vs radical resection: no difference in 5 year survival; less local recurrence in radical resection for T2 cancer (P:0.04). Less complication, transfusion and Length of hospital stay in TEM **Case series**: reported varying results due to different cancer stages, study population, full excision, adjuvant therapy and treatment indication	**I** The aim of cancer surgery is to balance the risk of disease recurrence against quality of life and non cancer related death. The introduction of TEM has greatly increased the utility of local excision as a curative procedure. Cancer outcomes in selected tumours are comparable to RR but without the associated morbidity or mortality. TEM is also associated with less anorectal and genito-urinary dysfunction and better quality of life. These factors should be considered when deciding optimal treatment option in select patients groups such as tumours with low risk of recurrence or high risk procedures in elderly patients who have significant risk of dying from non cancer related disease. There is sufficient evidence to justify a prospective randomised trial comparing TEM + ∕ - neo-adjuvant therapy against RR in selected patients and tumour types. Unlike previous trials, the outcome should not just emphasis cancer recurrence rates but should also include immediate and long-term morbidity, gastrointestinal function and quality of life.

Quality assessment: bibliographic search: databases reported and key words reported. No language restriction. Not specified if studies were assessed for inclusion and data extracted by two independent reviewers. Inclusion criteria clearly stated. Methodological quality of primary studies considered but not assessed using validated checklist. Number of included and excluded studies reported.

Quality of reporting (QUOROM checklist)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE,
	Date restriction	Up to June 2006
	any restriction	No language restriction
Selection	Inclusion and exclusion criteria	Comparative and individual studies publishing results of TEM in adenoma and carcinoma. Studies had to report at least one of the following primary outcome measures: local recurrence rate, systemic recurrence, overall ∕ disease-free survival or probability of survival
Validity assessment	Criteria and process used	Methodological quality of primary studies considered but not assessed using validated checklist
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis nor performed
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results presened narratively

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Lezoche 2008	To compare the oncologic results for local excision via (TEM) and those for laparoscopic resection (LR) via total mesorectal excision in the treatment of T2 N0, G1-2 rectal cancer after neoadjuvant therapy with both treatments, RCT Italy	70 patients whose malignancy was staged at admission as T2 N0, G1-2 rectal cancer located within 6 cm of the anal verge with a tumour diameter less than 3 cm.	Experimental: TEM (n.25) Control: laparoscopic total mesorectal excision (n.35)	Local recurrence Distant metastases Survival Length of hospital stay Blood loss Analgesic consumption Postoperative complication	5 year	Median operative time TEM: 90 min (range, 90–100 min), LR:173 min (range, 160–200 min) P<0.001 Hospital stay (days): median (25–75th %tile) TEM 3 (3–6) LR: 7 (5–8) P<\0.001c Transfusions: TEM: 0 LR:23% P<0.001a Analgesic: TEM: 14% LR: 100% P<0.001 Postoperative complication: no significant difference Local recurrence: TEM: 5.7% LR: 2.8% Distant metastases: TEM: 5.7% LR: 2.8%	**II** The long-term results of the current study indicate that for selected patients who have T2 N0 rectal cancer treated with preoperative high-dose radiochemo-therapy and TEM, it is possible to achieve the same longterm oncologic results observed after laparoscopic resection with total mesorectal excision in terms of probability for local failure and survival. There is, however, the need for multicenter, randomised controlled trials to answer the many questions concerning the treatment of T2 rectal cancer using preoperative radiochemo-therapy and TEM.

Quality assessment: allocation concealment: unclear; double blinding: not possible but not relevant for objective outcomes.

8.4 Management of other screen-detected cancer

8.4.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 4

How should other screen detected cancers be treated?

PICOS

P: All patients with screen detected cancers
I: Multidisciplinary management
C: Non multidisciplinary management
O: Rate of recurrence, disease specific survival
S: Systematic reviews and guidelines

GUIDELINES

We found five guidelines, three UK (1,4,5) and two US (2,3).

All of the guidelines on the management of colorectal cancer (except the NICE Technology Appraisal 105 Guidelines) agree that a multidisciplinary approach is necessary for managing colorectal cancer. A comprehensive risk assessment is advocated by all the guidelines, which should include assessment of family history. Indeed, pathological assessment of the lesions/s was deemed crucial when deciding the appropriate management strategy for a patient. Furthermore, the histological features were also stated as vitally important when assessing risk. There is general consensus on pathological reporting of:

      a. Grade of cancer (TNM system)
      b. Depth of penetration
      c. Number of lymph nodes evaluated and number of positive nodes
      d. Status of radial margins

Excision by colonoscopic polypectomy is recommended for lesions where there is a low risk of malignancy. Laparosopic surgery is recommended as a treatment option for colorectal cancer in all guidelines.

For high-risk, advanced rectal cancer the general consesus supported transabdominal resection.

For high-risk, advanced colon cancer the general consesus supported colectomy with en bloc resection in the US guidelines and primary resection in the UK guidelines

Quality of guidelines

Generally, the retrieved guidelines were of good quality and complied with the majority of the methodological quality criteria for guidelines. The SIGN Guidelines were excellent; they were the only guidelines which complied with all respective quality criteria. As such, greater consideration should be given to guidelines of better quality.

REFERENCES

1. Guidelines for the Management of Colorectal Cancer 2007 The Association of Coloproctologists of Great Britain and Ireland.

2. NCCN Clinical Practice Guidelines in Oncology Colon Cancer V.1.2008

3. NCCN Clinical Practice Guidelines in Oncology Rectal Cancer V.1.2008

4. Management of Colorectal Cancer - A National Clinical Guideline - SIGN, 2003 Produced by: Scottish Intercollegiate Guidelines Network (SIGN) - March 2003 No.67

5. Laparoscopic Surgery for Colorectal Cancer Produced by: National Institute for Health and Clinical Excellence (NICE), April 2006. Technology Appraisal 105

8.4.2 Evidence tables

Author, publication year	Study design	Recommendation	Level of evidence Strength of recommendation
Association of Coloproctologists of Great Britain and Ireland. Colorectal cancer management Issue date: August 2007	Clinical guideline	**Access to Treatment** i) Treatment should begin within 31 days of discussion with the patient of the decision to treat. B ii) All patients with colorectal cancer should have the benefit of a suitably informed surgical opinion and their management should be discussed by the multidisciplinary team. **C** iii) Patients with colorectal cancer should have access to a colorectal nurse specialist for advice and support from the time they receive the diagnosis. iv) It is important that patients with colorectal cancer are offered the opportunity to ask questions and to have important information repeated. Provision of information should be an essential part of every consultation **C** **Preparation for Surgery** i) All patients undergoing surgery for colorectal cancer should give informed consent. Informed consent implies being given information about the likely benefits and risks of the proposed treatment and details of any alternatives. Informed consent should be obtained by the operating surgeon where possible. **C** ii) The patient who may require a stoma should be seen by a stoma nurse prior to surgery and t the referral should be made at the earliest opportunity to allow adequate time for preparation **C** iii) Bowel preparation should not be used routinely before colorectal cancer resection. **B** iv) A combination of graduated compression stockings and heparin should be used for thrombo-prophylaxis for patients undergoing colorectal surgery. **A** v) All patients undergoing surgery for colorectal cancer should have antibiotic prophylaxis. A single dose of appropriate intravenous antibiotic is likely to be effective. **A** **Elective Surgical Treatment** i) It is recommended that the term curative resection should be based on surgical and histological confirmation of complete excision. Surgeons should expect to achieve an overall curative resection rate of 60%, but it is appreciated that this will depend at least in part on the stage at which patients present. **B** ii) Any cancer whose distal margin is seen at 15 cm or less from the anal verge using a rigid sigmoidoscope should be classified as rectal. **C** iii) It is recommended that total mesorectal excision should be performed for cancer in the lower two-thirds of the rectum, either as part of a low anterior resection or an abdomino-perineal resection (APER). In tumours of the upper rectum the mesorectum should be divided no less than 5 cm below the lower margin of the tumour. Care should be taken to preserve the pelvic autonomic nerves and plexuses, and perforation of the tumour during operation should be avoided. **B** iv) If a surgeon has any doubt regarding the choice of operation between low anterior resection or abdomino-perineal excision of the rectum, an experienced second opinion should be sought. **B** v) Surgeons should expect to achieve an operative mortality of less than 20% for emergency surgery and less than 7% for elective surgery for colorectal cancer. **B**	**Grading of Evidence** **Ia:** Evidence obtained from meta-analysis of randomised controlled trials **Ib:** Evidence obtained from at least one randomised controlled trial **IIa:** Evidence obtained from at least one well-designed controlled study without randomisation **IIb:** Evidence obtained from at least one other type of well-designed quasi-experimental study **III:** Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case studies **IV:** Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities **Grading of Recommendations** **A:** Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation (levels Ia, Ib). **B:** Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (levels IIa, IIb, III) **C:** Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable clinical studies of good quality (level IV)

Author, publication year	Study design	Recommendation	Level of evidence Strength of recommendation
		vi) Surgeons should carefully audit their leak rate for colorectal surgery, and should expect to achieve an overall leak rate below 8% for anterior resections and below 4% for other types of resection. Ultra-low pelvic anastomoses are associated with a higher leak rate, and the judicious use of a temporary defunctioning stoma is recommended. **B** vii) Local excision for cure in rectal cancer should be restricted to T1 cancers less that 3cm in diameter with good or moderate differentiation. It must be accepted that subsequent histopathological examination of cancers thought to be suitable for local excision will identify a proportion which require more radical surgery. B viii) All laparoscopic colorectal operations should be performed by surgeons properly trained in colorectal surgery. These surgeons should also have undergone preceptorship laparoscopic training, particularly in rectal procedures. Their results should be carefully audited in the local hospital multidisciplinary setting and should also be submitted to the Association of Coloproctology of Great Britain and Ireland colorectal cancer database. **A**	

Quality assessment: description of the multidisciplinary panel provided; method of literature retrieval and assessment not reported but it is stated that a comprehensive literature search has been performed. Method used to reach consensus not reported. Level of evidence and grading of recommendation provided. Reference list reported.

Author, publication year	Study design	Evidence	Conclusion
NICE Technology Appraisal Guidelines 105 Laparoscopic surgery for colorectal cancer Issue date: August 2006	Systematic review of RCTs for NICE Guidance	Systematic reviews identified 19 randomised controlled trials (RCTs) that were relevant to the appraisal. An unpublished meta-analysis based on individual patient data (IPD) from a subset of patients (n = 1536) from four RCTs was also considered. This independent meta-analysis was submitted by a manufacturer consultee before publication on an academic-in-confidence basis, and the results are not presented in this document. When compared with open surgery, laparoscopic surgery was associated with a statistically significant longer operating time (weighted mean difference [WMD] 40 minutes, 95% confidence interval [CI] 32 to 48 minutes, based on three RCTs) and shorter hospital stay (WMD 2.6 days, 95% CI 2.0 to 3.1 days, based on four RCTs). The results with laparoscopic resection also suggested a trend towards a decreased number of lymph nodes retrieved (WMD −0.4, 95% CI −1.4 to 0.6 nodes, based on three RCTs), an increased risk of anastomotic leakage (pooled relative risk [RR] 1.13, 95% CI 0.74 to 1.73, based on eight RCTs), and a decreased risk of operative and 30-day mortality (based on three RCTs) compared with open resection, although these differences did not reach statistical significance. RCTs and the IPD meta-analysis reported overall survival. Raw data were available from six RCTs and contributed to a meta-analysis that did not show a statistically significant difference in overall survival between laparoscopic and open resection (pooled RR 1.03, 95% CI 0.98 to 1.09). However, these RCTs had widely differing follow-up periods that ranged from 1 to 108 months, and proportion of events rather than time-to-event data were analysed. Three-year survival outcomes from the seventh RCT (the CLASICC trial) have not been published and only very limited information about these results was available. Five RCTs and the IPD meta-analysis reported disease-free survival. Raw data were available from four RCTs – meta-analysis of these data did not show a statistically significant difference between laparoscopic and open surgery (pooled RR 1.01, 95% CI 0.95 to 1.07). Long-term survival outcomes in the fifth RCT (the CLASICC trial) have not been published and only very limited information about these results was available. Seven RCTs and the IPD meta-analysis contained relevant information on tumour recurrence. Two of the RCTs reported zero event rates in both surgery groups. In a meta-analysis of the remaining five studies, there was no statistically significant difference between the two types of surgery (pooled RR 0.92, 95% CI 0.74 to 1.14). Eight RCTs contained information on port-site recurrence. There were only three reported events. Some patients who were originally randomised to undergo laparoscopic surgery were converted intra-operatively to open resection. Eleven RCTs reported conversion rates: the mean overall rate was 20%. Three RCTs recorded separate outcome data for converted patients who appeared to have higher blood loss, require a longer hospital stay and have a greater risk of tumour recurrence than patients who	Laparoscopic surgery is recommended as an option for patients with colorectal cancer. Guidance applies to patients that would be considered suitable for both treatment options. The decision on which procedure should be undertaken should be made after an informed discussion between patient and surgeon. The following should be considered: _Risks and benefits of both procedures _Suitability of lesion for laparoscopic surgery _Experience of the surgeon in both procedures

Author, publication year	Study design	Evidence	Conclusion
		underwent the laparoscopic or open procedure as planned. Anastomotic leakage was the only outcome for which there were sufficient data to conduct a stratified meta-analysis by location of cancer (that is, to establish differences in clinical effectiveness for cancers of the colon and rectum). The increased risk of anastomotic leakage with laparoscopic resection compared with open resection was similar for colon and rectal cancers (pooled RR for colon cancer 1.27, 95% CI 0.70 to 2.31, four studies; pooled RR for rectal cancer 1.25, 95% CI 0.63 to 2.46, two studies). Only 2 RCTs reported subgroup analyses by stage of cancer for overall survival. Both reported that there was no statistically significant difference in overall survival between patients undergoing laparoscopic surgery and those undergoing open surgery for cancer stages I, II or III. Submissions from manufacturer and professional consultees contended that long-term clinical outcomesbetween open and laparoscopic colorectal surgery are equivalent, while short-term clinical outcomes favour the laparoscopic approach.	

Quality assessment: A list of members of the appraisal committee members and their institutional affiliations is documented in the guidelines and the member's clinical interests are available from the NICE website. An assessment report was prepared which details search strategy (databases, years), inclusion and exclusion criteria and methods of analysis. Sources of evidence used are described as are consideration of the evidence by the committee. Grades of recommendation and levels of evidence are not provided, although details of the implementation of the guidelines into clinical practice are described. A list of references is provided.

Author, publication year	Study design	Recommendation	Level of evidence / Strength of recommendation

SIGN
Mangement of colorectal cancer
 	
Issue date: 2003
	Clinical guideline	**Preoperative staging**
		All patients undergoing elective surgery for colorectal cancer should have preoperative imaging of the liver and chest. **B**
		In patients requiring emergency surgery intraoperative liver ultrasound or postoperative imaging is acceptable **B**
		Complete colonic examination by colonoscopy, CT pneumocolon or barium enema should be carried out, ideally preoperatively, in patients with colorectal cancer **C**
		
		Preparation for Surgery
		Patients undergoing surgery for colorectal cancer should have:
		    - venous thomboembolism prophylaxis,
		    - antibiotic prophylaxis consisting of a single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia. **A**
		If a patient undergoing colorectal cancer surgery is deemed to require a blood transfusion, this should not be withheld on account of a possible association with increased risk of cancer recurrence**. B**
		
		Elective Surgical Treatment
		<u>Rectal cancer</u>
		Mesorectal excision is recommended for most rectal cancers where the patient is fit for radical surgery. The mesorectal excision should be total for tumours of the middle and lower thirds of the rectum, and care should be taken to preserve the pelvic autonomic nerves wherever this is possible without compromising tumour clearance (**B**)
		With a low rectal anastomosis, consider giving a defunctioning stoma **(C)**
		With a low rectal anastomosis after TME, consider a colopouch **(C)**
		The relative risks of operative morbidity and recurrence must be carefully weighed and explained fully to the patient so that an informed decision can be made regarding local excision and rectal cancer **(C)**
		Further surgery for pedunculated polyp cancers is indicated if:
		    - there is histological evidence of tumour at, or within 1 mm of, the resection margin;
		    - there is lymphovascular invasion;
		    - the invasive tumour is poorly differentiated**(C)**
			Levels of evidence
			
			| 1++
				High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion	 **Grades of recommendations** **A:** At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

Author, publication year	Study design	Recommendation	Level of evidence Strength of recommendation
			B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ **C:** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++ **D**: Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+ **Good practice points:** Recommended best practice based on the clinical experience of the guideline development group

Quality assessment: description of the multidisciplinary panel provided; method of literature retrieval and assessment not reported but it is stated that a comprehensive literature search has been performed. Method used to reach consensus not reported. Level of evidence and grading of recommendation provided. Reference list reported.

8.5 Management of incomplete adenoma excision

8.5.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 5

How should incomplete adenoma excision be managed ?

PICOS

P: All patients with evidence of incomplete adenoma excision
I: Endoscopic treatment
C: Surgery
O: Rate of recurrence
S: Any Study

SEARCH METHOD

Searches were conducted for primary studies on Medline, Embase and for systematic reviews on The Cochrane Library including only studies published between 2000 and 2008

MedLine and Embase:
(("Colorectal Surgery"[Mesh] OR "Colorectal Surgery/surgery"[Mesh])) AND ("Adenoma"[Mesh] OR ("Adenoma/complications"[Mesh] OR "Adenoma/surgery"[Mesh]))
Postoperative AND incomplete adenoma removal
colonoscopy AND adenoma AND polypectomy surveillance AND adenoma surveillance
large colorectal polyps AND colonoscopy AND management
colonoscopy AND adenoma excision
colonoscopy AND adenoma excision AND recurrence AND incomplete
incomplete adenoma excision AND large sessile adenoma
endoscopic treatment of large sessile and flat colorectal lesions
incomplete removal AND adenomas

We also looked at the references of retrieved articles to find other relevant paper

RESULTS

No systematic reviews were located.

We found two studies (1,2) dealing with treatment of incomplete removal of polyps and three studies already considered for question 1 which also reported the results of treatment of incomplete adenoma excision.

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8.5.2 Evidence tables

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Brooker 2002	The aim of this study was to evaluate the safety and efficacy of argon plasma coagulation (APC) in preventing recurrence when applied to the edge and base of the polypectomy site after apparently complete piecemeal resection. RCT UK	21 patients with large (>1.5 cm) sessile polyps removed by piecemeal snare cautery and judged to have been completely resected with the snare. Complete snare resection was not possible in a further 13 polyps (13 patients), for which APC therapy was used without regard to randomization.	Experimental. APC after complete piecemeal polypectomy n.10 Ctrl. no APC after complete piecemeal polypectomy n.11 APC after incomplete polypectomy .n.13	Complication recurrence	1 year	<u>Recurrence</u> APC after complete resection: 10% No APC after complete resection: 63.6% P: 0.02 APC after incomplete resection: 46% <u>Complication</u>: bleeding APC after complete resection: 0% No APC after complete resection: 9% APC after incomplete resection: 38.% Overall: 17.6%	**II** In patients with apparent complete endoscopic snare resection of large adenomas, postpolypectomy application of APC reduces adenomatous recurrence. Even when complete snare resection was not possible, the use of APC prevented recurrence in 54% of patients. Because recurrence was still sometimes seen after APC, including 1 case after apparently complete snare resection, stringent follow-up is essential

Quality assessment allocation concealment unclear. Blinding of provider not possible, blinding of patients not relevant, blinding of outcome assessor not relevant objective outcome. None lost at follow up.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Follow up	Results	Level of evidence Conclusions
Regula 2003	To evaluate the long term outcomes of argon plasma coaguation (APC) to an adjunt to piecemeal polypectomy for large sessile adenomas case series Poland	77 patients with 82 sessile adenomas (median size: 2.9 cm)	Snare piecemeal technique without saline injection. In case of complete polypectomy no further treatment was performed. In case of incomplete polypectomy an ACP was performed immediately and repeated at 1-2 days intervals until complete eradication. Patients were follow by regular follow up with colonoscopy and biopsy every 3 months for the first year and every 6 months the second years. In case of recurrence patients were retreated with ACP. Surgery was used when carcinoma was found or no perceivable benefits was seen on repeated treatment sessions	Completion of excision Complication recurrence	Median : 38 months	Completion of excision after piecemeal polypectomy: 18% 82% of patients required the ACP treatment immediately after the polypectomy (58.8%) or after the first follow up colonoscopy with biopsy (41.2%) Eradication histologically proven: Only polypectomy: 100% Polypectomy +ACP:90% Recurrence: Only polypectomy group: 14% Polypectomy +ACP:14% Complication: Only polypectomy group: 7% Polypectomy +ACP:14%	V ACP is an effective and safe procedure for treating incomplete excision of sessile adenomas. ACP should repeated until complete eradication is confirmed. Intensive follow up every 3 month is mandatory

8.6 Criteria for postponing polypectomy in patients taking anticoagulants/ antiaggregants

8.6.1 Summary document

Silvia Minozzi and Jo Watson

CLINICAL QUESTION 6

Which are patient-related criteria for postponing polypectomy in asymptomatic people undergoing CRC screening and taking anticoagulants/antiaggregants)?

PICOS

P: General population at average risk of colorectal cancer aged 50 years and older taking anticoagulants or antiaggregants
I: Polypectomy during flexible sigmoidoscopy or colonoscopy
C: Not applicable
O: Safety, adverse effects, complication
S: Systematic reviews of observational studies, case series, prospective or retrospective cohort studies, case-control studies

SEARCH METHOD

In the first instance systematic reviews have been searched. Because the retrieved reviews didn't specify the date of the bibliographic search, we searched all the primary studies published since 2000.

Quality assessment of systematic reviews was done using a simplified version of the QUOROM Statement checklist. Quality assessment of case control studies was done using the Newcastle-Ottawa scale.

Search strategy:

MedLine: Search date 15th October 2007

Search Terms (("Colonic Polyps/surgery"[Mesh]OR "polypectomy" free text) AND ("Postoperative Complications"[Mesh] OR Gastrointestinal Haemorrhage"[Mesh])), Limits: Publication Date from 2000 to 2007

RESULTS

Two reviews published in 2006 and 2007 were identified. One assessed the risk of bleeding in patients taking anticoagulants and antiplatelet therapy (1), the other assessed the risk of bleeding only in patients taking antiplatelet therapy (2). The reviews were of poor methodological quality: the search

strategy was described only in one (1), dates of the search strategy were not specified, inclusion criteria of primary studies were not specified, Quality assessment of primary studies was not performed, number of studies retrieved, included and excluded were not specified, characteristics of primary studies were described in only one review (2).

The reviews concluded that the use of anticoagulants (warfarin) significantly increases the risk of immediate and delayed bleeding after polypectomy. The summary estimate of thromboembolic and haemorrhagic events cannot be accurately made for patients using LMWH for periprocedural anticoagulation. The studies assessing the risk of bleeding in patients taking aspirin or other NSAIDs did not show any significant increase in the risk of bleeding, but the safety of antiplatelet therapy in patients undergoing gastrointestinal endoscopic procedures remains unproven. Large multicenter randomised controlled studies are needed in order to draw firm conclusions.

We found three case series (3,4,5) assessing the risk of bleeding in patients taking warfarin. Two case series included very few participants (21 and 51 patients). In the first study no cases of bleeding were found, in the second study 1/51 cases was noted. The third study (5) included 1657 patients treated with polypectomy out of which 17 were taking warfarin. The risk of post-polypectomy bleeding was significantly higher among patients who had received warfarin before colonoscopy: OR 13.37 (95%CI 4.10-43.65).

We found two (5,6) studies assessing the risk of bleeding in patients taking antiplatelet agents: one case control study and one case series. The case control study didn't find any increase of risk of bleeding in patients taking aspirin: OR=1.41 (95%CI 0.68-3.04) or other NSAIDs: OR=0.90 (95%CI 0.36-2.23). The case series included 1657 patients treated with polypectomy out of which 219 were taking antiplatelet therapy. There were 37 cases of bleeding. In this group 16% of patients were taking aspirin or NSAID. In the non bleeding group 13% of patients were taking aspirin or NSAID (p=0.62). There was no increase in the risk of post-polypectomy bleeding associated with the use of aspirin and/or NSAIDS.

Finally we found one cross-sectional study (7) which assessed the risk factors for immediate bleeding in a sample of 5152 patients treated with polypectomy. The use of anticoagulants was associated with increased risk (OR 3.71 (CI95% 1.05-13.05)) but not the use of aspirin or NSAIDs.

CONCLUSIONS

Very few studies assessed the risk of bleeding in patients taking anticoagulants or antiplatelet therapy and the studies were of poor methodological quality. From the available evidence we can conclude that the use of anticoagulants (warfarin) is associated with a significantly increased risk of bleeding, while the use of aspirin or other NSAIDs is not. The following points must be considered when determining the management of patients taking anticoagulants or antiplatelet therapy: the risk of discontinuing anticoagulation, the bleeding risk associated with polypectomy, the morbidity and mortality rates of thromboembolic complication versus those of bleeding complications, the timing of cessation and reinstitution of anticoagulants or antiplatelet therapy.

Warfarin should be discontinued 3-5 days before the procedure. Patients with high risk of thromboembolic events should receive subcutaneous LMWH which should be stopped at least 8 hours before the procedure. LMWH could be resumed 6 hours after the procedure. Another possibility is to perform an initial diagnostic colonoscopy followed, if necessary, by a second colonoscopy for polypectomy using LMWH bridge therapy.

If the high risk of thromboembolism is potentially transient, (eg: deep venous thrombosis) the best option would to delay the polypectomy until the risk is decreased (LEVEL OF EVIDENCE :IV,V).

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8.6.2 Evidence tables

Author, publication year	Study design	Intervention	Participants	Outcome	Follow up	Results	Level of evidence onclusions
Makar GA, 2006	Systematic review	Endoscopy Polypectomy	Patients taking anticoagulatns or antiplatelet agents who performed endoscopic poypectomy	Adverse events: acute and delayed bleeding		A case control studies with patients who not stopped warfarin therapy yeld an OR of 13.37 (95%CI 4.1-14.36) of postpolypectomy bleeding. Several observational studies reported data on the use of LMWH for periprocedural anticoagulation but summary estimate of thromboembolic and haemorrhagic events cannot be accurately reported. Two case control studies of postpolypectomy bleeding did not demonstrated a significant association between aspirin or NSAID exposure and risk of postpolypectomy bleeding. There are not published data regarding the safety of thienopyridines during endoscopy.	IV, V The following things must be considered when deciding the management of patients taking anticoagulants or antiplatelet therapy : the risk of discontinuing anticoagulation, the bleeding risk associated with polypectomy, the morbidity and mortality rates of thromboembolic complication versus those of bleeding complications, the timing of cessation and reinstitution of anticoagulants or antiplatelet therapy.Guidelines of the American Society of Gastrointestinal Endoscopy (2002) recommend that warfarin should be discontinued 3-5 days before the procedure. Patients with high risk of thromboembolic events should receive subcutaneous LMWH which should be stopped at least 8 hours before the procedure. LMWH could be resumed 6 hours after the procedure. Another possibility is to perform an initial diagnostic colonoscopy followed, if necessary by a second colonoscopy for polypectomy using LMWH bridge therapy.If the high risk of thromboembolism is potentially transient, (es: deep venous thrombosis) the best option would to delay the polypectomy until the risk is decreased. If a decision is made to withhold a therapy with thienopyridines before performing polypectomy, these agents need to be discontinued 7-10 days before the procedure.

SR polypectomy in anticoagulated patients – Makar 2006

Quality of reporting (QUOROM CHECKLIST)

METHODS	DATABASES , REGISTER, HAND SEARCHING;	MEDLINE, REFERENCE LIST OF RETRIEVED ARTICLES; CONTACT WITH AUTHORS;
SEARCH	Date restriction	Until June 2005
	any restriction	Only English language articles
Selection	Inclusion and exclusion criteria	Not stated
Validity assessment	Criteria and process used	Not done
Data abstraction	Process used	Not stated
Quantitative data synthesis	Measures of effect, method of combining results	RR, Peto Odds Ratio;
Results Trial flows	Trial flow and reason for exclusion	no
Study characteristics	Type of studies, participants, interventions, outcomes	no
Study results	Descriptive data for each trial	Only for some studies
Methodological quality	Summary description of results	no
Quantitative data synthesis	Agreement on the selection and validity assessment;	no
	summary results	Narrative description of the results

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence
Kimchi, N.A. 2007	Narrative Review.	Endoscopy Polypectomy	Polypectomy related bleeding AND Patients taking antiplatelet agents who performed endoscopic poypectomy	Adverse events: immediate and delayed bleeding	Rates of polypectomy related bleeding in 4 studies(use of aspirin not specified in the studies): Sieg(2001):14.249 patients; 0.11% major bleeding events Nelson(2002): 1.672 patients;0.36% major bleeding events Rosen(1993): 4.721 patients; 0.42% major bleeding events Gibbs(1996): 13 major bleeding events out of 6365 polypectomies[1] Studies looking at aspirin/NSAID use prior to polypectomy: Shiffman(1994): 694 patients. Prospective case series Patients (%) with major delayed bleeding – among aspirin/NSAID users – 2/46 (4.3% – among control group – 2/648 (0.3%) Non-significant difference between groups Hui(2004): 1.657 patients; retrospective case series. Patients (%) taking aspirin or NSAID – In bleeding group – 6/37 (16%) – In non-bleeding group – 213/1620 (13%) Non-significant difference (p=0.62) Yousfi(2004): 162 patients; case control study Patients (%) taking aspirin or NSAID – In bleeding group – 32/81 (40%) – In non-bleeding group – 27/81 (33%) OR 1.4; 95% CI 0.68-3.04	**IV, V** The safety of antiplatelet therapy in patients undergoing gastrointestinal endoscopic procedures remains unproved. Large multicenter randomised controlled studies are needed in order to draw firm conclusions. *Colonoscopy* In many patients, it seems reasonable to stop aspirin before the procedure because: (1) the risk of polypectomy-related major bleeding is not negligible (up to 0.42% in recent series) and there is no sufficient data regarding the safety of aspirin use in this setting, and (2) in contrast to EGD, the prevalence of colonic polyps requiring removal is high and it is important to spare the patient the possibility of a second procedure if a polyp is found. *Aspirin Withdrawal Period* When aspirin is indicated for primary prevention, we recommend stopping this drug 5–7 days before colonoscopy. When the indication is secondary prevention, it is probably appropriate to shorten this period to 3 or 4 days. In patients in whom the antiplatelet treatment is for primary prevention, we think that aspirin use should be avoided for 2 weeks after UGI or colonic polypectomy. In others cases, the risk of delayed bleeding (e.g. by the polyp characteristics) and the cardiovascular risk of aspirin withdrawal should be assessed in order to define the management. When the cardiovascular risk is high, aspirin should be resumed probably no more than 1 week after the polypectomy. If a patient has not complied

with the request to withdraw aspirin before a colonoscopy, it is reasonable to remove polyps unless they are 1 15 mm, especially if sessile. After the procedure, this patient should be requested not to resume aspirin for 1–2 weeks, as mentioned above.

NSAID Withdrawal Period
Non-selective NSAIDs should be stopped 8 h before any endoscopy. After a polypectomy, it seems reasonable to not resume treatment with these drugs for 7–14 days. The use of COX-2 inhibitors carries no risk in this setting.

Clopidogrel (Plavix) Withdrawal Period
Based on the available limited information, we propose to stop clopidogrel, 5 days before colonoscopy. If the patient is with a recent coronary stent, it seems reasonable to postpone the colonoscopy if the indication is not urgent.

SR polypectomy in anticoagulated patients – Kimchi 2007

Quality of reporting (QUOROM CHECKLIST)

METHODS	DATABASES , REGISTER, HAND SEARCHING;	NOT STATED
SEARCH	Date restriction	Not stated
	any restriction	Not stated
Selection	Inclusion and exclusion criteria	Not stated
Validity assessment	Criteria and process used	Not stated
Data abstraction	Process used	Not stated
Quantitative data synthesis	Measures of effect, method of combining results	Results from original studies restated No attempt made to combine results
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	No
Study results	Descriptive data for each trial	For some studies
Methodological quality	Summary description of results	No
Quantitative data synthesis	Agreement on the selection and validity assessment;	No
	summary results	Narrative description of the results

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Friedland 2006	Polypectomy with standard cautery After polypectomy 1 or 2 slips placed prophylactically	Case series	21 Patients in therapy with warfarin without discontinuation until 36 hours before the procedure. Average polyps size: 5.0mm (range 3-10 mm)	Bleeding or other complications	3 to 8 weeks	No episodes of bleeding or other complications.	V

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Timothy 2001	Colonoscopy with either hot biopsy or snare polypectomy	Case series	109 participants. Warfarin stopped 2 or 3 days before the procedure; patients maintained on continuous infusion of intravenous heparin qhich was stopped 1 or 2 hours before the procedure and restarted 1 hour after. 51 patients had either hot biopsy or snare polypectomy	Bleeding or other complications	2 months	1/51 (1.95%) patient who underwent hot biopsy had haemorragic complication 1 week after the procedure	V

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Hui 2004	Colonoscopy, which in some cases involved electrosurgical polypectomy.	Retrospective case series	5593 colonoscopy patients. 1657 of the colonoscopies involved polypectomy Patients taking antiplatelet therapy: 219. Patients taking warfarin : 17	Bleeding episodes, either immediate or delayed and graded as 'mild', 'moderate' or severe.	30 days	37 cases (2.2%) of post polypectomy bleeding were recorded (32 immediate, 5 delayed) 31 of the immediate bleeds were 'mild' and 1 'moderate'. Of the 5 delayed bleeds, one was 'mild', two were 'moderate' moderate and one was 'severe'. Patients taking aspirin or NSAID in bleeding group: 16% Patients taking aspirin or NSAID in non bleeding group: 13%. (p=0.62). There was no increase in the risk of post-polypectomy bleeding associated with the use of aspirin and/or NSAIDS . Patients taking warfarin in bleeding group: 10.8% Patients taking warfarin in non bleeding group: 0.8% (p<0.001). The risk of post-polypectomy bleeding was significantly higher among patients who had received warfarin before colonoscopy. The risk remained after adjustment for other factors: OR 13.37 (95%CI 4.10-43.65) In univariate analyses comparing patients with or without post-polypectomy bleeding, there was no difference with regard to gender, size of the largest polyp, or location of polyps. Patients with bleeding were significantly older than those without.	**V** The main finding of the present study was that the use of antiplatelet agents and NSAIDs alike is not associated with an increased frequency of post-colonoscopic polypectomy bleeding. In contrast to antiplatelet agents, the results of the present study show that anticoagulants, such as warfarin, should be stopped and the INR (international normalised ratio) normalised before performing an elective colonosopy in which therapeutic manoeuvres are anticipated.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Yousfi 2004	Colonoscopy and polypectomy Aspirin exposure within 3 days prior to polypectomy	Case control study	Cases: identified from 4 Mayo Clinic databases, presented with clinically significant postpolypectomy bleeding after colonoscopy and polypectomy Controls: identified from same databases as cases – had undergone colonsopic polypectomy without any complications (Patients with heparin or warfarin use within 24 hours of polypectomy were excluded from the analysis)	Clinically significant post-polypectomy bleeding after colonoscopy and polypectomy.	30 days	81 cases vs 81 controls Number of patients exposed to aspirin: Bleeding – 32, control – 27 OR=1.41 (95%CI 0.68-3.04 p=0.36) Number of patients exposed to NSAID: Bleeding – 11, control – 13 OR=0.90 (95%CI 0.36-2.23 p=0.82)	IV The safety of endoscopic polypectomy in patients taking aspirin remains controversial.

Quality assessment: adequate definition of the cases with independent validation; Controls selected from the same hospital as the cases; Adjustment for the most important and other factors; Ascertainment of exposure by reviewing the medical records of the patients; Same method of ascertainment for cases and controls; Both groups had no non-responders.

Author, publication year	Screening test evaluated Comparator test	Study design	Participants	Outcome	Follow up	Results	Level of evidence
Kim 2006	Colonoscopic polypectomy.	Prospective cross-sectional study	5,152 patients treated by polypectomy	Risk factors for immediate postpolypectomy bleeding.	n/a	215 cases (4.2%) of post polypectomy bleeding. Risk factor for bleeding: age: ≥ 65 vs <65 OR 1.37 (CI95%1.02-1.83 Anticoagulants: OR 3.71 (CI95% 1.05-13.05) polyps size: >1 cm vs ≤ 1cm: OR2.38 (CI95%1.78-3.18) chronic renal disease: OR 3.29 (CI95%1.84-5.87) cardiovascular disease: OR 2.08 (CI95%1.45-2.99) Aspirin or NSAID use was not associated with increased risk of bleeding	V

8.7 Cold snare and hot biopsy with diminutive polyps

8.7.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 7

Is there any difference in complication (bleeding) and quality of sample between cold snare and hot biopsy for removal of small polyps (<1 cm)?

PICOS

P: Patients with small polyps (<1cm) undergoing polypectomy
I: Cold snare
C: Hot biopsy
O: Complication (bleeding); quality of sample for histology
S: RCTs, comparative non-randomised studies, case series

SEARCH METHOD

Searches were conducted for primary studies on MedLine and Embase without data restriction. The following search strategies were used:

("cold snare" OR "hot biopsy") AND polypectomy
"cold snare" OR "hot biopsy"
diminuitive polyps" AND ("snare" OR "hot biopsy")

RESULTS

Deenadayalu 2005 (1) determined the retrieval rates of polyps after cold snaring with two different methods of resection and retrieval on 400 polyps with mean size of 3.5 mm in case series. There were no significant difference in the retrieval rate and no complication occurred. The quality of samples for histology was not assessed. Authors concluded that cold snare removal of colon polyps is associated with a high polyp retrieval rate. Each of two methods of polyp retrieval was effective.

Parra-Blanco 2000 (2) assessed the incidence and nature of complications when polypectomy is performed with different types of hot biopsy in 4,735 polyps; mean size was not reported. Quality of sample for histology was not assessed Authors concluded that polypectomy can be performed with pure cut current with a bleeding rate comparable to that seen with the use of coagulation or blended current, provided that hemoclip placement can be used readily.

Goldstein 2001 (3) evaluated the relationships between coagulation-induced thermal artifacts in hot biopsy and polyp size in 119 colonic polyps, 5 mm or less in maximum dimension. Lack of definitive diagnosis due to cytologic artifacts was observed in 16.5% (range, 11.8%-19.3%). Decreasing polyp

size, analysed as a continuous variable, was associated significantly with the inability to make a diagnosis owing to cytologic artifacts. Authors concluded that decreasing polyp size was associated linearly with the inability to make a definitive diagnosis owing to cytologic artifacts caused by thermal elettrocoagulation. Polyps smaller than 2 mm significantly more often could not be definitively diagnosed by at least 1 pathologist owing to cytologic artifacts.

Uno 1997 (4) assessed the correlation between polyp size and bleeding after cold snare excision of polyps with up to 7 mm of size in a case series. Mean bleeding time increased with polyp size and lasted up to 6 minutes for 6 mm polyps. It took 10 minutes and required electrocoagulation for polyps of 7 mm diameter. The quality of the sample for histology wasn't assessed. Authors concluded that cold snare is a safe method for polyps up to 6 mm in size.

Paspatis 2005 (5) compared the efficacy and safety of cold biopsy followed by bipolar electrocoagulation using large probes (10 Fr) and high power setting to conventional monopolar hot biopsy forceps in the eradication of 75 diminutive rectal adenomas (up to 5 mm in maximum dimension) in 50 patients in a randomised controlled trial. There were no significant differences in the frequency of residual adenoma tissue. No complications occurred in either group. The quality of the sample for histology was not assessed. Authors concluded that cold biopsy followed by bipolar electrocoagulation using large probes and high power settings for destroying diminutive rectal adenoma seems to be equally effective and safe as conventional monopolar hot biopsy forceps in the eradication of diminutive rectal adenomas.

Fry 2006 (6) assessed the diagnostic quality of polyps obtained by snare polypectomy using two different electrosurgical currents (hot biopsy) in 148 polypectomies performed in 116 patients. Average polyps size was 13.5 mm. Author concluded that more extensive tissue damage occurred using the conventional ESG than when using Endocut. The overall quality of the polypectomy specimens was better using Endocut. Finally, the ability to evaluate resected polyp margins and overall tissue histology was better with the microprocessor-controlled ESG than with the conventional ESG.

Weston 1995 (7) assessed the risk of perforation and haemorrage in the treatment of diminutive polyps with cold biopsy (436) or hot biopsy (1,525 polyps) in a retrospective case series. Significant haemorrhage occured in six cases in which hot biopsy was used. The risk of hot biopsy-induced haemorrhage was significantly higher in the right colon than in the transverse colon and left colon (p <0.05). the rate of haemorrage with cold biopsy is not reported in the abstract and we were not able to retrieve the full text. The author concluded that the decision to use the hot biopsy or cold biopsy technique to eradicate diminutive polyps should take into account the location of the polyp because of the significantly increased risk of haemorrhage with hot biopsies in the right colon.

CONCLUSIONS

Seven studies have been retrieved assessing the outcomes of cold snare or hot biopsy for diminutive polyps. Three studies were case series of hot biopsy (2,3,6); two of them assessed the quality of tissue for histological diagnosis; one found that the ability to evaluate resected polyp margins and overall tissue histology was better with the microprocessor-controlled ESG than with the conventional ESG. The other study found that decreasing polyp size was associated linearly with the inability to make a definitive diagnosis owing to cytologic artifacts caused by thermal electrocoagulation. Polyps smaller than 2 mm significantly more often could not be definitively diagnosed by at least 1 pathologist owing to cytologic artifacts. The third study found no difference in bleeding rate using three different types of electrocoagulation (LEVEL OF EVIDENCE V).

Two studies were case series of cold snare (1,4). None of them assessed the quality of sampling for histological evaluation. One found that mean bleeding time increased with polyp size and lasted up to 6 minutes for 6 mm polyps. The other study assessed the retrieval rate of polyps with two different types of cold snare and found no statistically significant difference (LEVEL OF EVIDENCE V).

Two studies compared hot biopsy vs cold biopsy. One was a retrospective case series and found that the risk of bleeding with hot biopsy is significantly higher in the right colon. Only one RCT (5) with 50 patients was found comparing the efficacy and safety of cold biopsy with hot biopsy. No conclusion can be drawn for the comparison of quality of sampling for histology because this outcome wasn't assessed. Cold biopsy followed by bipolar electrocoagulation using large probes and high power setting for destroying diminutive rectal adenoma seems to be equally effective and safe compared to conventional monopolar hot biopsy forceps in the eradication of diminutive rectal adenomas (LEVEL OF EVIDENCE II).

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8.7.2 Evidence tables

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Deenadayalu 2005	To determine the retrieval rates of polyps after cold snaring with two different methods of resection and retrieval. retrospective review of case series USA	400 polyps with mean size of 3.5 mm	Cold snare polypectomy by two methods: Method A was cold snare resection without tenting, with subsequent suctioning of the transected polyp into the trap. Method B was by ensnaring the polyp and pulling it into the colonoscope channel followed by transection of the polyp with simultaneous suctioning	Retrieval rate complication	Retrieval rate Method A: 100% Method B: 98% Complication: 0	**V** Cold snare removal of colon polyps is associated with a high polyp retrieval rate. Each of two methods of polyp retrieval was effective. No complications occurred

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Parra-Blanco 2000	To study the incidence and nature of complications when polypectomy is performed with a pure cut current retrospective review of case series Japan	4,735 polyps mean size not reported	Electrosurgical polypectomy using pure cut current. The method of polypectomy ("hot" biopsy, snare polypectomy or EMR) was chosen according to the size and endoscopic features of the polyp. Hemoclips were placed after polypectomy to prevent bleeding at the discretion of each endoscopist	Bleeding	Bleeding: snare polypectomy 0.9%, EMR :1.6%, "hot" biopsy 0.4%, piecemeal polypectomy 7.3%.	**V** Polypectomy can be performed with pure cut current with a bleeding rate comparable to that seen with the use of coagulation or blended current, provided that hemoclip placement can be used readily

Tutta hot biopsy

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Goldstein 2001	To evaluate the relationships between coagulation-induced thermal artifacts, polyp size, and interobserver diagnostic variation among 3 pathologists in diminutive polyps retrospective review of case series	119 colonic polyps, 5 mm or less in maximum dimension	Hot biopsy : The polyp was grasped, oriented, and pulled toward the lumen by a 2.2-mm cup, Microvasine Endoglide thermal electrocautery forceps. Slight pulling force was applied to the polyp while electrical current was on for several seconds until a white coagulum was seen at the polyp base, and the polyp was severed from the stalk.	Lack of definitive diagnosis because of cytologic artifacts Factors associated with artifatcs	52.9% of polyps were smaller than 2 mm. 15.1% were resected without thermal electrocoagulation. Lack of definitive diagnosis because of cytologic artifacts: 16.5% (range, 11.8%-19.3%). Decreasing polyp size, analysed as a continuous variable, was associated significantly with the inability to make a diagnosis owing to cytologic artifacts by each pathologist and by any of the pathologists (P = .022). The type of thermal electrocoagulation, including blended or cutting, and current setting were not associated with the inability to make a definitive diagnosis (P = .08-.41). Among polyps smaller than 2 mm in maximum dimension, a definitive diagnosis could not be made by at least 1 pathologist because of marked cytologic artifacts in 2 (20%) of 10 polyps that were excised without thermal electrocautery (cold cup), compared with 23 (45%) of 51 polyps that were excised with thermal electrocautery (P = NS).	**V** Decreasing polyp size was associated linearly with the inability to make a definitive diagnosis owing to cytologic artifacts caused by thermal elettrocoagulation. Polyps smaller than 2 mm significantly more often could not be definitively diagnosed by at least 1 pathologist owing to cytologic artifacts,,

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Uno 1997	To evaluate the correlation between polyps size and bleeding after cold snare excision retrospective review of case series China	80 patients with 80 colonic polyps, less than 1 cm in maximum dimension	Cold snare excision	Bleeding time	Polyp size of 7mm or more: hemostasis took 10 minutes and required electrocoagulation. Polyp size of 1-2 mm: 0.3 – 2 min Polyp size of 3 mm: 0.5 – 3.2 min Polyp size of 4 mm: 2 – 4 min Polyp size of 5 mm: 2 – 6 min Polyp size of 6 mm: 3 – 6 min Bleeding at follow up (10 days): none	V CSE is a safe method for polyp up to 6 mm of size.

Author, publication year	Study objective Study Design	Study Participants	Intervention	outcomes	Results	Level of evidence Conclusions
Paspatis 2005	To compare the efficacy and safety of cold biopsy followed by bipolar electrocoagulation using large probes (10Fr) and high power setting to conventional monopolar hot biopsy forceps in the eradication of diminutive rectal adenomas RCT Grece	50 patients with 75 rectal polyps, up to 5 mm in maximum dimension	Group A: cold biopsy followed by repeated gold probe electrocoagulation using a 10 Fr catheter with setting 8 (40 W) for 1 second (n.24) Group B: conventional monopolar hot biopsy forceps (n.26)	Residual adenoma tissue complication	Residual adenoma tissue Group A: 5.2% Group B: 10.8% (P: NS) Complication: none	**II** Cold biopsy followed by bipolar electrocoagulation using large probes and high power setting for destroying diminutive rectal adenoma seems to be equally effective and safe as conventional monopolar hot biopsy forceps in the eradication of diminutive rectal adenomas.

Quality assessment: allocation concealment: unclear; blinding of provider: not possible; blinding of patients; not relevant; blinding of outcome assessor: unclear; none lost at follow up.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Fry 2006	To assess and compare the diagnostic quality of polyps obtained by snare polypectomy using two different electrosurgical currents (hot biopsy) case series USA	148 polypectomies in 116 patients. Average polyps size: 13.5 mm	Polypectomy using either blended EC with a conventional electrosurgical generator (ESG) or using an ESG with a microprocessor that automatically controls cutting and coagulation (Endocut).)	Margin evaluability overall quality of polyps	Had better margin evaluability Endocut 75.7% ESG: 60.3%, ($p = 0.046$). The overall tissue architecture was similar in both groups. Polyps removed with blended current had less overall quality as compared to polyps removed by Endocut ($p = 0.024$).	**II** More extensive tissue damage occurred using the conventional ESG than when using Endocut. The quality of the polypectomy specimens was overall better using Endocut. Finally, the ability to evaluate resected polyp margins and overall tissue histology was better with the microprocessor-controlled ESG than with the conventional ESG.

Author, publication year	Study objective Study Design	Study Participants	Intervention	Outcomes	Results	Level of evidence Conclusions
Weston 1995	To assess the complication rate of treatment of diminutive polyps with hot biopsy or cold snare Case series	1,525 polyps were removed by hot biopsy, 436, were removed by cold biopsy	Polypectomy using either blended EC with A conventional electrosurgical generator (ESG) or using an ESG with a microprocessor that automatically controls cutting and coagulation (Endocut).)	Perforation haemorrage	Perforation. None Haemorrage: significant haemorrhages in six cases in which hot biopsy was used. The risk of a significant haemorrhage from hot biopsy of diminutive polyps was 0.39%. The risk of hot biopsy-induced haemorrhage was significantly higher in the right colon than in the transverse colon and left colon (p <0.05). The risk in the cecum was 1.33%; in the ascending colon it was 1.03%, and for the remainder of the colon it was 0.24%.	**V** The decision to use the hot biopsy or cold biopsy technique to eradicate diminutive polyps should take into account the location of the polyp because of the significantly increased risk of haemorrhage with hot biopsies in the right colon.

8.8 Efficacy of radiotherapy for T1 rectal cancer after local excision

8.8.1 Summary document

Rita Banzi

CLINICAL QUESTION 8

What is the efficacy of radiotherapy for T1 rectal cancer after local excision?

PICOS

P: Patients with T1 rectal cancer treated by local excision (TEM included)
I: Radiotherapy after local excision
C: No radiotherapy; radical surgery
O: Recurrence, complication
S: RCTs, comparative non-randomised trials, case series

SEARCH METHOD

We searched MedLine from 1998 to 2009 using the following search strategy:
Rectal neoplasms (Mesh) AND radiotherapy (Mesh) AND ("local excision" OR "polypectomy" OR "early cancer" OR "T1 carcinoma"). We also checked the reported bibliography for further studies.

RESULTS

We found a low quality systematic review of observational studies (1) and two subsequent retrospective cohort studies (2, 3) relevant for this issue.

The systematic review by Sengupta et al. was aimed at assessing the available evidence on local excision of rectal cancers and included 14 observational studies in which postoperative adjuvant chemoradiotherapy was added to local excision. No meta-analysis was performed but a summary of finding is reported in Tables 2 and 3.

Table 2.
Local Excision with Postoperative Adjuvant Therapy

Reference	No.	Stages			Surgery (%)	Adjuvant Radiotherapy	Adjuvant Chemotherapy (%)	Follow-Up	Local Recurrences (%)	Distant Metastases (%)	Survival (%)
		T1	T2	T3							
Russell et al. 2000[31]	51*	13	25	13	TA (89) TSa (11)	50–56Gy (≥T2, poor histology), 59.4–65 (margin <3 mm)	5-FU (100)	6.1 yr (5–8.8)	13.7	13.7	5-yr DFS 75
Chakravarti et al. 1999[32]	47	14	33	0	TA/TSp (88) TSa (10)	53.6Gy (45–64.8) + boost to tumor bed	5-FU (54)	51 month (4–162)	10	NS	5-yr DFS 74
Graham et al. 1999[33] and 1994[34]	16*	2	9	5	TA/TSa	45Gy/5 wk + 9Gy boost (T3, N1, poor histology)	5-FU (100)	56 month (48–71)	0	12	5-yr actuarial 90
Le Voyer et al. 1999[54]	35*	15	16	4	TA/TSa	53Gy (>T1/poor histology)	5-FU (40)	46 month (8–120)	11.4	8.6	5-yr DFS 91
Steele et al. 1999[36]	51	0	51	0	TA/TSa	54Gy/5 wk	5-FU (100)	48 month	13.7	9.8	6-yr actuarial 85
Varma et al. 1999[37]	19*	4	9	6	NS	Dose NS (preop 25)	5-FU (73)	6 yr (0–16.6)	0	5	NS
Wagman et al. 1999[55] and Minsky et al. 1994[56]	39	6	25	8	TA (70) TSa (23)	>45Gy (82 boost 10Gy)	5-FU (66)	41 month (9–131)	21	15	5-yr actuarial 77
Taylor et al. 1998[32]	13	2	9	2	TA	45–55Gy	NS	52 month (14–115)	23	NS	NS
Bleday et al. 1997[57] and Jessup et al. 1992[41]	26*	0	21	5	TA (69) TSp (31)	54Gy	5-FU (100)	40.5 month	7.7	NS	NS
Valentini et al. 1996[58]	21*	9	12	0	TA	44.6Gy	0	54 month (18–128)	14	4.7	DFS at F/U 69.4
Fortunato et al. 1995[59]	21	2	15	4	TA (33 piecemeal)	5Gy preop and 50Gy postop	NS	55 month (27–92)	19	19	5-yr OS 77
Frazee et al. 1995[42]	11	9	2	0	TA	45–57Gy	0	30 month	0	9	OS at F/U 90
Ota et al. 1992[60]	46	16	15	15	TA/TSp/TSa	45Gy/5 wks	5-FU (17)	36 month (18–73)	8.7	13	DFS at F/U 86
Coco et al. 1992[44]	15*	0	15		TA	47Gy	0	68 month (≥24 month)	6	6	5-yr actuarial 74

NS = not stated; TA = transanal; TSp = transsphincteric; TSa = transsacral; DFS = disease-free survival; OS = overall survival; F/U = follow-up; preop = preoperatively; postop = postoperatively.
* Endorectal ultrasound used as part of staging.

Table 3.
Local Excision with Preoperative and/or Postoperative Adjuvant Therapy for Some Patients

Reference	No.	Stages			Surgery	Adjuvant Radiotherapy	Adjuvant Chemotherapy	Follow-Up (Range)	Local Recurrence	Distant Metastases	Survival (%)
		T1	T2	T3							
Benoist et al. 1998[61]	30	19	8	3	TA	23.3	NS	57 month (6–145)	13	6.7	OS at F/U 60
Baron et al. 1995[62]	91	42	34	11	TA/TSp/TSa	52.7 (30.7 preop)	0	55.3 month	21	NS	5-yr DFS 86.4
Read et al. 1995[63]	22	13	6	3	TA	45 (22 postop, 15 preop, 9 sandwich)	4.5	63 month (16–115)	9.1	4.5	OS at F/U 72
Willett et al. 1994[64]	46	34	12		TA/Tsp (80) TSa (18)	54 (45 Gy)	NS	48 month	18	12	5-yr actuarial 72
Rouanet et al. 1993[65]	18	13	5	0	NS	Some	0	61 month (24–144)	11	0	OS at F/U 100
Bailey et al. 1992[66]	53	NS	NS	0	TA	64 (45 to 50Gy)	NS	44 month (12–130)	8	1.8	5-yr DFS 90
DeCosse et al. 1989[67]	57	25	28	3	NS (9 → radical)	Some (preop and postop)	0	NS	NS	NS	5-yr DFS 83.4

NS = not stated; TA = transanal; TSp = transsphincteric; TSa = transsacral; DFS = disease-free survival; OS = overall survival; preop = preoperatively; postop = postoperatively.
* Endorectal ultrasound used as part of staging.

The two subsequent retrospective cohort studies (2, 3) were performed in South Korea and reported unclear data.

Min et al.(2) analysed 76 patients who underwent local excision for distal rectal adenocarcinoma with curative intent and found a 5-year local recurrence-free survival rate (LFS) of 89.4% in the

pT1 group and 75.0% in the pT2 group (p=0.012). Among the patients with pT1 cancer, those who received adjuvant radiation therapy demonstrated a 5-year LFS of 100%, compared to those who did not, 76.0% (p=0.038).

Park et al.(3) retrospective study attempt to clarify the role of adjuvant radiotherapy in reducing local recurrence in patients with stage 2 rectal cancer. This study included 390 stage T2 rectal cancer patients identified by the colorectal cancer database who underwent curative resection (TEM) followed by adjuvant therapy. Radiotherapy did not seem to provide additional benefit in decreasing local recurrence rate of stage IIA rectal cancers over chemotherapy alone (local recurrence:

chemotherapy plus radiotherapy: 6 (3.6%); chemotherapy: 5 (2.7) p=0.96. Radiotherapy had no effect on local recurrence-free survival rate or on overall disease-free survival and 5-year survival rates.

CONCLUSIONS

Preoperative or neoadjuvant therapy for rectal cancer is based on the concept of tumour down-staging before surgery. However, there are limited data on its use for local excision of rectal cancer. The limited data available do not allow a valid assessment of the efficacy of preoperative radiotherapy and local excision of rectal cancer. The published results suggest that local excision gives acceptable results after preoperative radiotherapy for postradiotherapy Stage T1 but not T3 lesions. The outcome for T2 lesions is not clear, and should be subject to further study. Adjuvant or neoadjuvant chemoradiotherapy seems to improve the prognosis after local excision. The absence of controlled data makes it difficult to compare directly the results of local excision with or without adjuvant therapy. There is a clear need for well-designed, randomised controlled trials to answer the questions surrounding the role of adjuvant radiotherapy after local excision of rectal cancer. The available evidence suggests that low-risk T1 tumours may be treated by local excision alone and T2 or high-risk T1 tumours will benefit from adjuvant chemo-radiotherapy following local excision. (1) (LEVEL OF EVIDENCE III,V)

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8.8.2   Evidence tables

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
Sengupta 2001	"Systematic review"	To examine current evidence on local excision of rectal cancers and how it fits into the management algorithm for rectal cancer	41 studies on curative local excision of rectal cancer published in English	local excision (LE) of rectal cancer	-	local recurrence rates	***Local recurrence rates*** <u>LE alone</u> T1: 9.7% (range, 0-24) T2: 25% (range, 0-67) T3: 38% (range, 0-100) <u>LE and adjuvant chemo-radiotherapy</u> T1: 9.5% (range, 0-50) T2: 13.6% (range, 0-24) T3: 13.8% (range, 0-50)	**V** Local excision for rectal cancers is associated with a low morbidity and provides satisfactory local control and disease-free survival rates for T1 rectal cancers. There is, however, a need for a randomised, controlled trial for T2 cancers, comparing local excision with adjuvant chemoradiotherapy to radical resection.

Quality of reporting (QUOROM CHECKLISt)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE
	Date restriction	Not specified
	any restriction	Not specified
Selection	Inclusion and exclusion criteria	Not specified
Validity assessment	Criteria and process used	Not specified
Data abstraction	Process used	Not specified
Quantitative data synthesis	Measures of effect, method of combining results	Meta analysis not performed
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	Yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	No
	summary results	No

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
Min 2007	Retro-spective cohort study	To review long-term oncologic results of local excision (LE) and to investigate the validity and feasibility of LE as a treatment option for distal rectal cancer	76 patients underwent LE for distal rectal cancer 11 cases of pTis, 47 cases of pT1, 16 cases of pT2, 2 cases of pT3 median age 60 years (range: 27–85 years) male-to-female ratio 36:40 Seoul, Korea	Local excision (LE) with or without radiotherapy	Median follow-up period 84.9 months	5-year cancer specific survival rate (CSR) 5-year local recurrence-free survival rate (LFS)	**5-year CSR** pT1: 81.2% pT2: 75.0% pT3: no survival p=0.001 **5-year CSR** Adjuvant radiotherapy: 100% No adjuvant radiotherapy: 76% pT3: no survival p=0.001 **5-year LFS** pT1: 89.4% pT2: 75.0% p=0.740 **pT1 5-year LFS** Adjuvant radiotherapy (N=11): 100% No adjuvant radiotherapy (N= 26): 83.8% p=0.036 **pT1 local recurrence** Adjuvant radiotherapy (N=11): - No adjuvant radiotherapy (N= 26): 3 (11.5) **pT1 systemic recurrence** Adjuvant radiotherapy (N=11): 2 (22.2) No adjuvant radiotherapy (N= 26): -	**III** These results imply a potential role of Local Excision and adjuvant radiation as an option for the treatment of distal rectal cancer, and that even for pT1 carcinoma, LE alone might not be a valid modality.

Quality assessment: retrospective design. Patient selection: not fully reported, unclear representativeness and ascertainment of exposure. No information on adjustment.

Author, publication year	Study design	Objective	Participants	Intervention	Follow up	Outcome	Results	Level of evidence Conclusions
Park 2008	Retrospective cohort study	To clarify the role of adjuvant radiotherapy in reducing local recurrence in patients with stage 2 rectal cancer	390 stage T2a rectal cancer identified by the colorectal cancer database who underwent curative resection (TEM) followed by adjuvant therapy Chemotherapy: 180 patients (46.2%), Chemo-radiotherapy: 210 patients (53.8%) Average patient age was 57 years (range, 19–78 years). from 1995 to 2002 South Korea	TEM with adjuvant Chemotherapy and chemotherapy plus radiotherapy	Mean follow-up period was 65 months (range, 2–133 months)	Local recurrence (LR) Time to recurrence (TTR)	Radiotherapy was performed significantly more commonly in younger patients (p = 0.01) and those with lower rectal cancer (p <0.001). **Overall recurrence** 62 recurrences occurred in 47 patients (12.1%). **LR** chemotherapy plus radiotherapy: 6 (3.6%) chemotherapy: 5 (2.7) p=0.96 Overall, radiotherapy had no effect on LR in patients with primary upper rectal (p = 0.48), midrectal (p = 0.74), or lower rectal (p = 0.97) tumours **Overall 5-year rate of freedom from local recurrence** 97.4% (95% CI, 115–123), **Overall 5-year survival rate** 91.6% (95% I, 118–125). Radiotherapy had no effect on local recurrence-free survival rate or on overall disease-free survival and 5-year survival rates.	**III** Radiotherapy did not seem to provide additional benefit in decreasing local recurrence rate of stage IIA rectal cancers.

Quality assessment: retrospective design. Patient selection: not fully reported, unclear representativeness and ascertainment of exposure. No information on adjustment.

8.9 Additional evidence tables prepared after December 2009

1. Borschitz T, Wachtlin D, Mohler M, Schmidberger H & Junginger T (2008), Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer, *Ann.Surg.Oncol*, vol. 15, no. 3, pp. 712-720.

2. Kuhry E, Schwenk W, Gaupset R, Romild U & Bonjer J (2008), Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials, *Cancer Treat.Rev.*, vol. 34, no. 6, pp. 498-504.

3. McArdle CS & Hole DJ (2004), Influence of volume and specialization on survival following surgery for colorectal cancer, *Br.J.Surg.*, vol. 91, no. 5, pp. 610-617.

4. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ & Sebag-Montefiore D (2009), Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial, *Lancet*, vol. 373, no. 9666, pp. 821-828.

5. West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ & Quirke P (2008), Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study, *Lancet Oncol*, vol. 9, no. 9, pp. 857-865.

6. You YN, Baxter NN, Stewart A & Nelson H (2007), Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database, *Ann.Surg.*, vol. 245, no. 5, pp. 726-733.

Author, publication year	Study Objective Study Design	Inclusion criteria	Intervention compared	Outcome	Results	Conclusion Level of evidence
Borschitz 2008	To assess the impact of neo adjuvant chemo-radiotherapy followed by local excision for advanced (≥T2) rectal cancer Systematic review	Inclusion criteria: studies that assessed curative LE after nCRT in patients with (≥T2) rectal cancer. Additional criteria were available data on clinical staging, before nCRT, and the evaluation of results on the basis of the postoperative histopathologic finding Furthermore, tumour, node, metastasis system classification had to be performed according to IUACA Joint Committee on Cancer guidelines Information on the performance of nCRT and follow-up constituted additional inclusion criteria.	Local excision after neo chemo-radiotherapy	Recurrence rate	N. of included studies: 6 retrospective and one prospective case series- Total n of patients: 237. Clinical staging before surgery of the 237 patients showed a cT1–2 tumour in 37 (16%), a cT2 in 81 (34%), and a cT3 category in 119 (50%) patients A histological complete response (ypT0) was noted in 22% (53 of 237), a partial response at the submucosa level (ypT1) in 19% (45 of 237), and a slight (ypT2) or missing response (ypT3) in 36% (85 of 237) or 14% (33 of 237) of cases Overall recurrence: 7% neither the studies we considered nor our own patients showed LR in CR (ypT0). In addition, patients with ypT1 tumour consistently showed low LR rates of 2% (range, 0%–6%), whereas in ypT2 findings, less favorable LR rates of 6% to 20% were observed, and disease that did not respond to therapy (ypT3) displayed LR rates in up to 42%.	**V** Despite of a highly selected patient collective, an extended indication for LE of cT2–3 rectal cancer after nCRT may be considered. The strongest prognostic factors were a CR (ypT0) or responses on submucosa level (ypT1). These first results will have to be confirmed in a prospective trial with an appropriate sample size to ensure high statistical power.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE
	Date restriction	1990 to 2007
	any restriction	Not reported
Selection	Inclusion and exclusion criteria	studies that assessed curative LE after nCRT in patients with (≥T2) rectal cancer. Additional criteria were available data on clinical staging, before nCRT, and the evaluation of results on the basis of the postoperative histopathologic finding Furthermore, tumour, node, metastasis system classification had to be performed according to IUACA Joint Committee on Cancer guidelines Information on the performance of nCRT and follow-up constituted additional inclusion criteria.
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	Meta analysis not performed
Results Trial flows	Trial flow and reason for exclusion	No
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	no
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	Results reported narratively

Author, publication year	Study Objective Study Design	Inclusion criteria	Intervention compared	Outcome	Results	Conclusion Level of evidence
Kuhry 2008	To evaluate the long-term results of laparoscopic and conventional colorectal resection. Cochrane Systematic review	Inclusion criteria: randomised controlled trials (RCTs) comparing laparoscopic(ally assisted) and open surgery for non-metastasised colorectal cancer randomised controlled trials (RCTs) comparing laparoscopic(ally assisted) and open surgery for non-metastasised colorectal cancer.	Laparoscopic versus conventional colorectal resection	Duration of follow-up, incidence of incisional hernia, incidence of reoperations for incisional hernia or intraperitoneal adhesions, incidence of local tumour recurrence, incidence of metachronous metastatic disease, location of metastases, overall mortality, cancer-related mortality, and recurrence-free and overall survival	Twelve trials (3346 patients) reported long-term outcome and were included in the current analyses. No significant differences were found between laparoscopic and open surgery in the occurrence of incisional hernias or the number of reoperations for adhesions (p = 0.32 and 0.30, respectively). Port-site metastases and wound recurrences were rare and no differences in occurrence after laparoscopic and open surgery were observed (p = 0.16). Cancer related mortality at maximum follow-up was similar after laparoscopic and open surgery (p = 0.15 and 0.16 for colon and rectal cancer, respectively).	I long-term outcome after laparoscopic surgery for colon cancer is no different to outcome after open surgery. For rectal cancer, the number of available studies and included patients is too low to draw any reliable conclusions. The results of large randomised studies will have to be awaited.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	COCHRANE LIBRARY, MEDLINE, EMBASE AND CANCERLIT . Eleven medical journals and abstracts from seven society meeting were hand-searched. The reference lists of all relevant articles were searched.
	Date restriction	1991 to 2005
	any restriction	No restriction
Selection	Inclusion and exclusion criteria	randomised controlled trials (RCTs) comparing laparoscopic(ally assisted) and open surgery for non-metastasised colorectal cancer randomised controlled trials (RCTs) comparing laparoscopic(ally assisted) and open surgery for non-metastasised colorectal cancer
Validity assessment	Criteria and process used	Validity ossesse using validated criteria
Data abstraction	Process used	Performde by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Mean differences with their corresponding 95% confidence intervals were used for the analysis of continuous variables. For dichotomous variables odds ratios with their 95% confidence intervals were calculated
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	Number of included studies and main characteristics reported.
Study results	Descriptive data for each trial	Yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Not reported
	summary results	yes

Author, publication year	Study Objective Study Design	Participants	Intervention	Outcome	Results	Conclusion Level of evidence
McArdle 2004	To establish whether differences in outcome following surgery for colorectal cancer among individual surgeons persisted after adjusting for case mix and known prognostic factors, and whether these differences were related to case volume or degree of specialisation. Retrospective (for 1991 and 1992 years) and prospective (for 1993 and 1994 years) cohort study	3,200 consecutive patients who underwent resection for colorectal cancer. Details included age, sex, extent of deprivation, mode of presentation, site of tumour, extent of tumour spread, Dukes' stage, the nature of surgery, postoperative (30 day) mortality, and the use of adjuvant therapy	To evaluate the effect of volume on outcome, surgeons were ranked on the basis of how many curative resections they performed during the study period. High volume group: Those treating more than 60 patients during the study period Medium volume group: those treating between 30 and 60 patients Low volume group: those treating fewer than 30 patients	Cancer specific survival at five years	Cancer-specific survival rate at 5 years following curative resection varied among surgeons from 53·4 to 84·6 per cent; the adjusted hazard ratios varied from 0·48 to 1·55. High volume group: 70·2 % , Medium volume group : 62·0 % Low volume group: 65·9 %. There were no consistent differences in the adjusted hazard ratios by volume. Specialists: 72·7 % Non specialists: 63·8 %; The adjusted hazard ratio for non-specialists was 1·35 (95 per cent confidence interval 1·13 to 1·62; $P = 0·001$).	**III** The differences in outcome following apparently curative resection for colorectal cancer among surgeons appear to reflect the degree of specialisation rather than case volume. It is likely that increased specialisation will lead to further improvements in survival

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage. None lost at follow up.

Author, publication year	Study Objective Study Design	Participants	Intervention	Follow up	Outcome	Results	Conclusion Level of evidence
Quirke 2009	Local recurrence rates in operable rectal cancer are improved by radiotherapy (with or without chemotherapy) and surgical techniques such as total mesorectal excision. However, the contributions of surgery and radiotherapy to outcomes are unclear. We assessed the effect of the involvement of the circumferential resection margin and the plane of surgery achieved.

Prospective cohort study | 1,156 patients with operable rectal cancer | plane of surgery achieved and the involvement of the circumferential resection margin were assessed by local pathologists, using a standard pathological protocol : Mesorectal, intramesorectal, muscularis propria plane of surgery | Three years | Local recurrence rate | 11% of patients had involvement of the circumferential resection margin, Mesorectal (good) plane of surgery achieved :52% intramesorectal (intermediate) plane of surgery achieved :34%), muscularis propria plane(poor):13%.
Both a negative circumferential resection margin and a superior plane of surgery achieved were associated with low local recurrence rates. Hazard ratio (HR) was 0·32 (95% CI 0·16–0·63, p=0·0011) with 3-year local recurrence rates of 6% (5–8%) and 17% (10–26%) for patients who were negative and positive for circumferential resection margin, respectively. For plane of surgery achieved, HRs for mesorectal and intramesorectal groups compared with the muscularis propria group were 0·32 (0·16–0·64) and 0·48 (0·25–0·93), respectively. At 3 years, the estimated local recurrence rates were 4% (3–6%) for mesorectal, 7% (5–11%) for intramesorectal, and 13% (8–21%) for muscularis propria groups. The benefit of short-course preoperative radiotherapy did not differ in the three plane of surgery groups (p=0·30 for trend). Patients in the short-course preoperative radiotherapy group who had a resection in the mesorectal plane had a 3-year local recurrence rate of only 1%. | **III**

In rectal cancer, the plane of surgery achieved is an important prognostic factor for local recurrence. Short-course preoperative radiotherapy reduced the rate of local recurrence for all three plane of surgery groups, almost abolishing local recurrence in short-course preoperative radiotherapy patients who had a resection in the mesorectal plane. The plane of surgery achieved should therefore be assessed and reported routinely. |

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage. None lost at follow up.

Author, publication year	Study Objective Study Design	Participants	Intervention	Follow up	Outcome	Results	Conclusion Level of evidence
West 2008b	To assess the quality of colon cancer surgery by studying the extent of variation in the plane of surgical resection, the amount of tissue removed, and its association with survival. Retrospective cohort study	399 patients who had resections for primary colon adenocarcinoma with curative or palliative intent. Excisions were excluded if they did not have adequate digital images to enable retrospective grading of the plane of mesocolic dissection. The quality of the mesocolic dissection was graded by use of the MRC CLASICC trial protocol depending on the plane of excision	Plane of surgery achieved and the involvement of the circumferential resection margin were assessed by local pathologists, using a standard pathological protocol: Mesorectal, intramesorectal, muscularis propria plane of surgery	Five years	Overall survival. Cox proportional hazards regression was used to study the association of patient, tumour, and surgical factors with survival	338 curative and 61 palliative excisions. muscularis propria : 24% intramesocolic 44% mesocolic 32% There was a 15% overall survival advantage at 5 years with mesocolic plane surgery compared with surgery in the muscularis propria plane (HR 0.57 [95% CI 0.38–0.85]); Statistical significance was lost in the multivariate model (HR 0.86 [0.56–1.31]). Association with improved survival and curative excisions was not signifcant in univariate (HR 0.72 [0.45–1.16],) or multivariate analysis (HR 0.70 [0.43–1.14]). A significant survival advantage in patients with stage III disease remained when the palliative excisions were removed in both univariate (HR 0.45 [0.23–0.86],) and multivariate analyses (HR 0.50 [0.26–0.98],). Patients with stage I and II disease (HR 0.84 [0.43–1.63],) and stage IV disease (HR 1.60 [0.64–3.99], did not show a significant survival advantage. Overall, there was a 4% difference in survival at 5 years between the muscularis propria and mesocolic planes in patients with stage I and II disease. None of the patients with stage IV disease were alive at 5 years.	III there is marked variability in the plane of surgery achieved in colon cancer. Improving the plane of dissection might improve survival.

Quality assessment : population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage. None lost at follow up.

Author, publication year	Study Objective Study Design	Participants	Intervention	Follow up	Outcome	Results	Conclusion Level of evidence
You 2007	To test the hypothesis that local excision is associated with compromised oncologic outcomes but reduced perioperative morbidity, when compared with Surgical Resection in rectal cancer Retrospective cohort study	1,094 patients with T1 and 1030 patients with T2 tumours malignant adenocarcinomas of the rectum	Local excision versus surgical resection	5-8 years	Morbidity (complications within 30 days of surgery leading to rehospitalisation), 5-year local recurrence 5-year overall survival	**30-day morbidity** LE 5.6% SR 14.6%; *P* <0.001. **5-year local recurrence** after adjusting for patient and tumour characteristics, T1 tumours: LE 12.5% SR 6.9% (*P* <0.003; hazard ratio :0.38; 95% CI, 0.23–0.62) T2 tumours LE: 22.1% SR 15.1% (*P*<0.01; hazard ratio :0.69; 95% CI, 0.44–1.07) **5-year overall survival** T1 tumours LE: 77.4% SR:. 81.7%, *P* : 0.09; T2 tumourse LE: 67.6% SR: 76.5%, *P* : 0.01)	**III** the proportion of patients with stage I rectal cancer treated by LE has dramatically increased over time. For patients with T1 rectal tumours, the selection for LE favored small, low-grade, distal tumours without evidence of invasion. Appropriately selected patients may expect acceptable OS after LE but experience a nearly 3-fold increased risk of local failure in the long-term, in exchange for reduced morbidities in the short-term. Thus, the decision regarding LE versus SR in this patient population requires an individualised analysis of the benefits and risks. For patients with T2 tumours, the selection for LE was highly restrictive based on both patient and tumour factors..

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage. Analysed only data of patients for whom follow up data were available.

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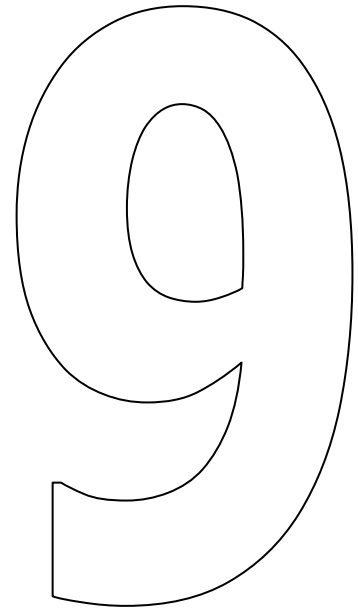
Colonoscopic surveillance following adenoma removal
EVIDENCE

EU CRC Guidelines Literature Group

9.1 Risk of neoplasia after a negative colonoscopy

9.1.1 Summary document

Silvia Minozzi

SEARCH METHOD

For all clinical questions we searched <u>MedLine</u> and <u>Embase</u> up to may 2008 using the following key words:

"Neoplasms recurrence, Local" Mesh AND "Colonoscopy" Mesh AND "Colorectal neoplasms" Mesh. To retrieve studies relating to question 1 we used the following strategy: ("Follow-Up Studies"[Mesh]) AND (("Colonoscopy"[Mesh]) AND ("Colorectal Neoplasms/epidemiology"[Mesh])). To retrieve studies relating to question 3 we used the following strategy: ((((("Adenomatous Polyps/surgery"[Mesh]) OR ("Colonic Polyps/surgery"[Mesh])) OR ("Colonoscopy"[Mesh])) AND ("Neoplasm Recurrence, Local"[Mesh])) AND ("Occult Blood"[Mesh]). To retrieve studies relating to question 2 we performed two additional searches with the following keywords: ("Colonoscopy"[Mesh]) AND ("Neoplasm Recurrence, Local"[Mesh]) AND ("Hyperplastic Polyps"); ("Colonoscopy"[Mesh]) AND ("Neoplasm Recurrence, Local"[Mesh]) AND ("Polyps"[Mesh]).

We also looked for recent high quality clinical practice guidelines on surveillance after polypectomy. We first searched for systematic reviews or clinical guidelines. We then searched for primary studies published after the more recent search of reviews or guidelines for questions covered by SRs or guidelines and without date restriction for questions not covered by SRs or guidelines.. For question 1 and 4 we considered studies already included in systematic reviews or guidelines because the original studies reported outcomes related to these questions which were not reported in the reviews or guidelines.

We found relevant articles for chapter 9 also performing a broader search on <u>MedLine</u> with the following strategy: (exp "Colorectal Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR colonic neoplasm* OR colonic tumour* OR colonic cancer* OR colorectal tumour* OR colorectal cancer* OR colorectal neoplasm* OR colonic polyp*) AND (exp "Colonoscopy"[Mesh] OR colonoscopy), limited to years 2007-2008

CLINICAL QUESTION 1

What is the risk of neoplasia after a negative colonoscopy?

PICOS

P: All individuals with a negative colonoscopy
I: Colonoscopy, sigmoidoscopy, FOBT
C: Not applicable
O: Rate of neoplasia
S: Observational studies

RESULTS

We retrieved 11 studies relating to question 1 (7,9,13,14,20,21,22,29,30,31,32). One is a narrative review (13) which has been considered because it reported the results of four primary studies which reported the incidence of adenomas after a negative colonoscopy. Six are retrospective studies (20,21,22,29,31, 32) and the other studies are prospective cohort studies reporting the results at follow up of subjects with negative baseline colonoscopy (7,9,14,31); one (30) is a case control study comparing the time of negative colonoscopy in patients with CRC detected because of symptoms or incidentally (rather than by screening) and in population based control subjects . Overall 15 primary studies have been identified. One study selected 29 patients with colorectal cancer who had one or more negative colonoscopies before the diagnosis, and assessed the stage of cancer and the interval between diagnosis and the previous examination (22).They concluded that size, differentiation and stage of colorectal cancer in addition to the interval to diagnosis suggest that the majority of cancers followed prior false negative examinations. The case control studies (30) found that after adjustment for the matching factors age and sex and other potential confounding variables, a previous negative colonoscopy was associated with a 74% lower risk of CRC (adjusted odds ratio adjOR=0.26 (95% CI, 0.16 to 0.40)). This risk reduction persisted throughout 20 years as demonstrated by the stratification of results with respect to the time interval of the last negative colonoscopy (1-2 years adjOR = 0.16 (95% CI 0.07-0.36); 3-4 years adjOR = 0.29 (95% CI 0.13-0.68); 5–9 years adjOR = 0.25 (95% CI 0.09-0.69); 10–19 years adjOR = 0.33 (95% CI 0.12-0.91); 20+ years adjOR = 0.46 (95% CI 0.16-1.32)). One retrospective cohort study (32) assessed the relative risk of any proximal or distal CRC in patients with negative colonoscopy compared with the general population. It found that the RR is substantially reduced for any proximal or distal neoplasia at 5,10 and 14 years of follow up but for proximal neoplasia the risk is not statistically significantly reduced in the first five years of follow up The other studies assess the incidence of neoplasia after a negative examination and their results are shown in the table below.

Primary studies which reported the incidence of adenoma and/or cancer

	Lieberman 2007	Neugut 1995	Yamaji 2004	Rex 1996 (data extracted from ref 13)	Squillace 1994 (data extracted from ref 13)	Hixon 1994 (data extracted from ref 13)	Huang 2001	Hooi 2001	Singh 2006	Lakoff 2008	Imperiale 2008
Participants	501	508	4084	154	29	58	362	1047	35975	110.402	1256
Follow up	5.5 years	3 years	3 years	5.6 years	5.7 years	2 years	4,3 years	5 years	Up to 10 years	7-14 years	5 years
Incidence of any adenoma		24% (Only 99 (19.4%)	20.8%	27%	41.4%	52%	21%				
Incidence of advanced neoplasia	2.4%		0.73%	0%		10%					1.3%
Cancer incidence								0.5%	SIR 0.69 (95% CI, 0.59-0.81) at 6 months, 0.66 (95% CI, 0.56-0.78) at 1 year, 0.59 (95% CI, 0.48-0.72) at 2 years, 0.55 (95% CI, 0.41-0.73) at 5 years, and 0.28 (95% CI, 0.09-0.65) at 10 years.	RR of any CRC at 5 years 0.56 (CI95%0.46–0.67) RR of any CRC at 10 years 0.45(CI95% 0.34–0.55) RR of any CRC at 14 years: 0.25 0.(CI95% 0.12–0.37)	0

CONCLUSIONS

It should be noted that in these studies the percentage of patients lost at follow up is quite high: in Neugut only 99 (19.4%) of patients without adenoma at index colonoscopy repeated the exam, in Liebermann the percentage of people lost at follow up is 28.6%, in Yamaji only 6,225 out of 68,053 who were first screened had at least three colonoscopies. This high percentage of drop out could bias the results. Moreover in Hixon also patients with adenoma/carcinoma at baseline have been included and this probably explains the high percentage of recurrence found in this study.

The incidence of any adenoma in patients with negative colonoscopy ranged from 20.8% to 52% and the incidence of advanced adenoma ranged from 0% to 10% with follow up ranging from 2 to 5 years. Cancer incidence ranges from 0 % to 0.55% at five years follow up in three studies and it has been reported as 0.28 (95% CI, 0.09-0.65) at 10 years in one study. In a third study RR of CRC in people with a previous negative colonoscopy compared to people with no colonoscopy has been reported for 110,402 patients as 0.56 at five years follow up, as 0.45 at 10 years follow up and as 0.25 at fourteen years follow up (LEVEL OF EVIDENCE III).

9.1.2 Evidence tables (see 9.8.2)

9.2 Risk of neoplasia after removal of hyperplastic polyps

9.2.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 2

What is the risk of neoplasia after removal of hyperplastic polyps?

PICOS

P: All patients with endoscopic removal of hyperplastic polyps
I: Colonoscopy, sigmoidoscopy, FOBT
C: Not applicable
O: Rate of neoplasia
S: Observational studies

RESULTS

We retrieved three studies that presented the results at baseline colonoscopy specifying the number of patients with hyperplastic polyps, but one did not report the results at follow up separately for this group of patients. The second study does not present results at follow up of patients who had a hyperplastic polyp removed at baseline, but the growth pattern is reported for adenoma and hyperplastic polyps less than 1 cm left in situ and followed up for three years in 58 patients (19). The

study found that both adenoma and hyperplastic polyps lesser than 5 mm tended to grow while the adenomas and hyperplastic polyps of 5-9 mm showed a reduction in size. Only one study (20) assessed the risk of neoplasia after the removal of hyperplastic polyps in 41 patients followed up for an average of 4.3 years. The rate of subsequent adenoma diagnoses was 42%.

CONCLUSIONS

The author of the only retrieved study which assessed the risk of neoplasia in patients who had hyperplastic polyps removed and were followed up for an average of 4 years concluded that patients found to have hyperplastic polyps at baseline may have twice the risk of adenomas on follow up as compared with those who have clean initial examinations. The study included only 42 patients so no definite conclusions can be made. (LEVEL OF EVIDENCE III)

9.2.2   Evidence tables (see 9.8.2)

9.3   Yield of FOBT after removal of adenomas

9.3.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 3

What is the yield of FOBT after removal of adenomas?

PICOS

P: All patients with endoscopic removal of adenomas
I: FOBT
C: Not applicable
O: Rate of neoplasia
S: Observational study

RESULTS

We found four studies (23,24,25,26) relevant for this question. One assessed the sensitivity of FOBT after resection of cancer or adenomas (23), the other three assessed the sensitivity and specificity of FOBT after the resection of cancer. The study which included patients who had adenomas removed presents their results together with results of patients who had curative resection of cancer. One study used the immunological test (25) and the others used the guaiac test (23,24,26). The sensitivity for any neoplasia is quite different among trials and are 0% and 18.5% for the guaiac test, 35.6% for the immunological test. The sensitivity for cancer is 100% for the immunological test and 22.7% and 43.5% for the guaiac test. The sensitivity for polyps or adenomas is 16.6% and 18.5% for the guaiac test and 24% for the immunological test. One study assessed the sensitivity for different types of

adenomas and found that the test was more sensitive with large and multiple adenomas, adenoma with villous component and severe dysplasia, but did not reach more than 40%.

	Jahn 1992	Hall 1999	Skaife 2003	Nava 1982
participants	529 patients with previous curative surgery for colorectal cancer. 279 patients with previous removal of adenomas	54 patients with previous curative surgery for colorectal cancer	611 patients with previous curative surgery for colorectal cancer	240 patients with previous curative surgery for colorectal cancer
FOBT	FOBT by Haemoccult II (three consecutive stool with dietary restriction and without rehydration)	FOBT by Haemoccult (six specimen with dietary restriction	Immunological FOBT	Haemoccult II FOBT (two specimen without dietary restriction)
Sensitivity for any neoplasia	17.3%	0%	35.6%	18.5%
Sensitivity for cancer	22.7%		100%	43.5%
Sensitivity for polyps or adenomas	16.6%		24%	18.5%

CONCLUSIONS

The guaiac test seems to be an unreliable test with very low sensitivity for detecting cancer or adenomas after curative resection of cancer. Authors of the studies concluded that this test should not be used to detect metachronus lesions. Immunological test seems to have better sensitivity to detect metachronus cancer but not adenomas. Authors suggest that the use of this test for surveillance could safely reduce the frequency of colonoscopy. (LEVEL OF EVIDENCE III)

9.3.2 Evidence tables (see 9.8.2)

9.4 Rate of neoplasia after endoscopic removal of adenomas

9.4.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 4

What is the rate of neoplasia after endoscopic removal of adenomas?

PICOS

P: All patients with endoscopic removal of adenomas
I: Colonoscopy
C: Not applicable
O: Rate of neoplasia
S: Observational study, RCT

RESULTS

We retrieved 11 studies relating to question 4 (6, 9, 10,11,14,16,17,18,27,28,33). Three are a prospective cohort study (9,14,28). One is a retrospective cohort study (6). Four (11, 16,18,27) have prospective cohort data drawn from all people enrolled in RCTs which showed no effect of the experimental intervention. One has prospective cohort data from an RCT on different screening surveillance protocols (17). One study reported the results of three RCTs which assessed the adenoma, advanced adenoma and cancer incidence /recurrence in people randomised to different follow up schedules and with different type of adenoma removed at index colonoscopy (10) . One is a case control study assessing the risk of CRC incidence up to ten year after removal of any polyp compared with the risk of CRC in a control population who never underwent a colonoscopy (33).

Study	Participants	Follow up	Any neoplastic lesion recurrence	Any Adenoma recurrence	Non advanced adenoma recurrence	Advanced adenoma recurrence	Cancer incidence
Neugut 1995	299 patients with adenoma at index colonoscopy	3 years		46% (only 59.5% of patients with adenoma repeated colonoscopy			
Le Bodic 2003	2,604 patients with a first adenoma removed	28 months (average)	28.3%				
Kronborg 2006 study 1	671 patients with peduncolated or small, flat and sessile adenomas up to 5 mm tubular or tubulovillous adenomas	Up to 20 years. Colonoscopy every 24 or 48 months		24 month s: 145/3000 p/y 48 months 123/2894 p/y		24 month : 22/3000 p/y 48 months : 24/2894 p/y	24 month: 1/3000 p/y 48 months: 6/2894 p/y
Kronborg 2006 study 2	73 patients with flat and sessile adenomas more than 5 mm and villous adenomas	Up to 14 years. Colonoscopy every 6 or 12 months		6 month 26/432 p/y 12 months 16/322 p/y		6 month: 3/432 p/y 12 months: 7/322 p/y	6 month: 1/432 p/y 12 months: 0/322 p/y
Kronborg 2006 study 3	200 patients with flat and sessile adenomas more than 5 mm and villous adenomas	Up to 20 years. colonoscopy every 12 or 24 months		12 month : 45/507 p/y 24 months: 41/525 p/y		12 month: 11/507 p/y 24 months l: 12/525 p/y	12 month: 2/507 p/y 24 months: 4/525 p/ye
Martinez 2001	1,287 participants who had at least one colonoscopy and had data on baseline characteristics of adenoma	3 years		48.6%		11.3%	

Study	Participants	Follow up	Any neoplastic lesion recurrence	Any Adenoma recurrence	Non advanced adenoma recurrence	Advanced adenoma recurrence	Cancer incidence
Laiyemo 2008	1,905 patients who had an adenoma removed at baseline and completed the trial	4 years		39.6%	33%	6.6%	
Lund 2001	776 participants who had adenoma removed at baseline	11 years	26.5%	26%			0.5%
Bonithon-Kopp 2004	552 participants who had adenoma removed at baseline and who completed the 3 years study	3 years		22.1%		7.4%	
Yamaji 2004	2,141 subjects with adenoma removed at baseline colonoscopy	3 years	30.8%				
Robertson 2005	2,915 patients who had an adenoma removed at baseline	3,7 years				0.25%(only adenoma with high grade dysplasia)	0.67%
Nozaki 1997	6,715 patients who had an adenoma removed at baseline	6 years	44.8%	44.2%		0.7% (only adenoma with high grade dysplasia)	0.63%
Joergensen 2007	2,041 patients who had an adenoma removal at baseline	Up to 24 years					RR: 0.65 (CI95% 0.43-0.95) compared to standard Danish population

CONCLUSIONS

The recurrence of any neoplastic lesions could be calculated only for four studies (12,236 participants) and ranged from 26.5% to 44.8%. The recurrence of any adenoma is reported in 6 studies (11,444 participants) and ranged from 22% to 48%. The recurrence of advanced adenoma is reported in 3 studies (3,744 participants) and ranged from 6% to 11%. Two studies reported onlu the recurrence of adenoma with high grade dysplasia which is 0.25% and 0.7%. The cancer incidence is reported in three studies (10,406 patients) and ranged from 0.5% to 0.67%. One study reported a RR of 0.65 (CI95% 0.43-0.95) of cancer incidence compared to standard population and a RR of CRC mortality of 0.12 (CI95% 0.03-0.36) .The data of the Kronborg study are difficult to compare with the other study results because it present the results in terms of person/years of observation (LEVEL OF EVIDENCE: III).

In the case control study, overall, subjects with a history of polypectomy up to 10 years had an about 60% lower risk of CRC than subjects without previous large bowel endoscopy (OR: 0.43 CI95% 0.25–0.74). The risk reduction is particularly high in the first 5 year after polyp removal (after 2 years OR: 0.16 CI95% 0.06–0.43; after 3-5 years: OR 0.27 CI95% 0.08–0.87) and becomes nonsignificant after 6-10 years follow up (OR: 1.90 CI95% 0.67–5.43) (LEVEL OF EVIDENCE IV).

9.4.2 Evidence tables (see 9.8.2)

9.5 Rate of recurrence

9.5.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 5

How is the rate of recurrence influenced by the characteristics of the adenoma removed (size, histology, number, dysplasia, location)?

PICOS

P: All patients with endoscopic removal of adenomas
I: Colonoscopy, characteristics of the adenoma removed (size, histology, number, dysplasia, location)
C: Not applicable
O: Rate of neoplasia
S: Observational study, RCT

RESULTS

We retrieved 10 studies relating to question 5 (1,2,6,7,10,11,33,35,36,37): Three (1,2,37) were systematic reviews assessing the risk of adenoma and advanced adenomas on the basis of characteristics of adenoma removed at baseline. We also included primary studies not yet included in

the systematic reviews. Two are retrospective cohort studies of 2,604 and 2,287 patients with a first adenoma removed (6,36), two are prospective cohort studies of 1,171 and 1,091 patients with neoplasia at baseline (7,35) and one is an analysis of prospective data from the Polyp Prevention Trial (11) and included 1905 patients who had an adenoma removed at baseline and completed the trial.

One study reported the results of three RCTs which assessed the adenoma, advanced adenoma and cancer incidence /recurrence in people randomised to different follow up schedules and with different type of adenoma removed at index colonoscopy (10). One is a case control study assessing the risk of CRC incidence up to ten year after removal of advanced or non advanced adenoma compared with the risk of CRC in a control population who never underwent a colonoscopy (33).

Systematic reviews

Risk factor	Winawer 2006	Saini 2006	Martinez 2001
Included studies	15 prospective studies (RCTs or observational) with at least 10 years follow up	15 prospective studies (RCTs or observational)	8 prospective studies (RCTs or observational)
Multiple adenomas (≥ 3):	multiplicity at baseline predict subsequent detection of <u>any adenoma.</u> Multiple adenoma predict subsequent detection of <u>advanced adenoma</u>	Multiplicity is a risk factor for any subsequent adenoma (meta-analysis not performed) Advanced adenomas (>3 vs 1-2) : RR 2.52 (CI95% 1.07-5.97)	<u>3 adenoma at baseline vs 1</u> Risk of non advanced adenoma OR 2.05 (CI95%1.73-2.42) Risk of advanced adenoma OR: 1.85 (CI95%1.46-2.34) <u>4 adenoma at baseline vs 1</u> Risk of non advanced adenoma OR 2.23 (CI95%1.71-2.92) Risk of advanced adenoma OR: 2.41 (CI95%1.71-3.40) <u>5+ adenoma at baseline vs 1</u> Risk of non advanced adenoma OR 3.63 (CI95%2.76-4.78) Risk of advanced adenoma OR: 3.87 (CI95%2.76-5.42)
Adenoma size (≥ 1 cm	adenoma >1 cm predict subsequent detection of <u>any adenoma</u> adenoma >1 cm predict subsequent detection of <u>advanced adenoma</u>	Adenoma size (>1 cm)is a risk factor for any subsequent adenoma (meta-analysis not performed) Advanced adenomas (≥ 1 cm vs <1cm) RR: 1.39 (CI 95% 0.86-2.26)	<u>10-20 mm at baseline vs <5mm</u> Risk of non advanced adenoma OR 0.94 (CI95%0.82-1.08) Risk of advanced adenoma OR: 2.27 (CI95%1.84-2.78) <u>>20 mm at baseline vs <5mm</u> Risk of non advanced adenoma OR 1.00 (CI95%0.80-1.25) Risk of advanced adenoma OR: 2.99 (CI95%2.24-4.00)
Tubulovillous histology	Tubulovillous histology predict the subsequent detection of <u>any adenomas</u> Tubulovillous histology predict the subsequent detection of <u>advanced adenomas</u>	Tubulovillous histology is a risk factor for any subsequent adenoma (meta-analysis not performed) Advanced adenomas :Tubulovillous histology vs tubular : RR : 1.26 (CI95% 0.95-1.66)	Risk of non advanced adenoma OR 1.05 (CI95%0.92-1.20) Risk of advanced adenoma OR: 1.28 (1 CI95%.07-1.52)
High grade dysplasia	High grade dysplasia predict the subsequent detection of adenomas High grade dyplasia predict the subsequent detection of advanced adenomas	High grade dysplasia is a risk factor for any subsequent adenoma (meta-analysis not performed) Advanced adenomas :High grade dysplasia vs no : RR: 1.84 (CI95% 1.06-3.19)	Risk of non advanced adenoma OR 1.04 (CI95%0.86-1.26) Risk of advanced adenoma OR: 1.05 (CI95%0.81-1.35)

Risk factor	Winawer 2006	Saini 2006	Martinez 2001
Proximal adenomas	Proximal adenomas predict the detection of <u>any adenomas</u> Proximal adenomas predict the detection <u>of advanced adenomas</u>	Proximal adenomas is a risk factor for any subsequent adenoma (meta-analysis not performed) Proximal adenomas is a risk factor for advanced adenomas (meta-analysis not performed)	Risk of non advanced adenoma OR 1.29 (CI95% CI95%1.16-1.44) Risk of advanced adenoma OR: 1.68 (CI95%1.43-1.98)

Primary studies

	Lieberman 2007	Le Bodic 2003	Kronborg 2006 study 1	Kronborg 006 study 2	Kronborg 2006 study 3	Laiyemo 2008	Nusko 2008	Cafferty 2007
Participants	1,171 with neoplasia at baseline	2,604 patients with a first adenoma removed	671 patients with peduncolated or small, flat and sessile adenomas up to 5 mm tubular or tubulovillous adenomas	73 patients with flat and sessile adenomas more than 5 mm and villous adenomas	200 patients with flat and sessile adenomas more than 5 mm and villous adenomas	1905 patients who had an adenoma removed at baseline and completed the trial.	1,091 patients with an adenoma removed and at least one follow-up examination. 573 had metachronous adenoma at surveillance	2,287 patients who received baseline colonoscopy and at least one colonoscopy at follow up.
Follow up	5.5 years	28 months (average)	Up to 20 years. Colonoscopy every 24 or 48 months	Up to 14 years. Colonoscopy every 6 or 12 months	Up to 20 years . colonoscopy every 12 or 24 months	3 years	Up to 25 years	Up to 28 years
Tub ad <1 cm: at baseline	Cumulative risk (CR)of advanced neoplasia 6.1% RR vs no neoplasia at beseline: 2.56							Tub or tub vill any size Risk of large polyp (≥10 mm) at follow up: OR: 0.66 (CI95% 0.23–1.94) vs none Risk of villous adenoma or cancer at follow up OR: 0.39 (CI95%0.10–1.53)
Tub ad>1 cm: at baseline	CR 15.5% RR:6.4					Size >1 cm vs <1cm: RR0.93 (CI95%0.61-1.41)		
Villous: at baseline	CR 16.1% RR:6.5			Any adenoma: 26/432 pers/yr (6 month) 16/322 p/y (12 months)	Any adenoma: 45/507 p/y (12 month) 41/525 p/y (24 months)	Villous component vs no villous component: RR2.25 (CI95%1.49-3.39)		Risk of large polyp (≥10 mm) at follow up: OR: 0.50 (CI95% 0.10–2.47) vs none

	Lieberman 2007	Le Bodic 2003	Kronborg 2006 study 1	Kronborg 006 study 2	Kronborg 2006 study 3	Laiyemo 2008	Nusko 2008	Cafferty 2007
				Advanced adenoma: 3/432 p/y (6 month) 7/322 p/y (12 months) Cancer: 1/432 p/y (6 months) : 0/322 p/y (12 months)	Advanced adenomas. 11/507 p/y (12 months) 12/525 p/y (24 months) Cancer: : 2/507 p/y (12 months) 4/525 p/y (24 months)			<u>Risk of villous adenoma or cancer at follow up </u>OR: 13.72 (CI95% 4.80–39.16) vs none
LGD at baseline:		CR of advanced adenoma or cancer :2.2%						
HGD: at baseline	CR 17.4% RR: 6.87	CR :4.2%				High grade dysplasia vs no: RR1.11 (CI95%0.64-1.90)	HDR vs LDS at baseline (RR 1.51; 95%CI 1.04–1.93)	
Cancer: at baseline	CR 34.8% RR: 13.56							
1-2 adenomas: at baseline	CR 6.5%							1 polyp at baseline vs none : OR 3.59 (CI95% 2.81–4.60) 2 polyps at baseline vs none: OR 6.46 (CI95% 4.73–8.83) <u>Risk of multiple polyp (≥3) at follow up</u> 1 polyp at baseline vs none: OR 2.94 (CI95%1.64–5.29) 2 polyps at baseline vs none: OR 6.91 (3.78–12.62)

	Lieberman 2007	Le Bodic 2003	Kronborg 2006 study 1	Kronborg 006 study 2	Kronborg 2006 study 3	Laiyemo 2008	Nusko 2008	Cafferty 2007
3-4 adenomas at baseline:	CR 15.9%					≥3 adenomas vs less: RR1.46 (CI95%0.96-2.2		≥3 polyps at baseline vs none: OR 13.72 (CI95% 9.88–19.06) <u>Risk of multiple polyp (≥3) at follow up</u> ≥3 polyps at baseline vs none: OR 20.97(12.14–36.22)
5-9 adenomas: at baseline	CR 17.2%							
10 + at baseline:	CR 12.5%							
<5 mm:		CR 1.5%	<u>Any Adenoma</u>: 145/3000 p/yr (24 month) 123/2894 p/y (48 months) <u>Advanced adenoma</u>: 22/3000 p/y (24 months) : 24/2894 p/y (48 months) <u>Cancer</u>: 1/3000 p/y : 6/2894 (48 months)					<u>Risk of large polyp (≥10 mm) at follow up:</u> OR 1.31 (CI95% 0.37–4.58)
5-20 mm		CR: 3%						
>20 mm:		CR 7%						
5-10 mm								<u>Risk of large polyp (≥10 mm) at follow up:</u> OR 6.07 (CI95% 1.86–19.82)

	Lieberman 2007	Le Bodic 2003	Kronborg 2006 study 1	Kronborg 006 study 2	Kronborg 2006 study 3	Laiyemo 2008	Nusko 2008	Cafferty 2007
>10 mm								Risk of large polyp (≥10 mm) at follow up: OR 9.98 (CI95%3.15–31.61)
>5 mm				Any adenoma: : 26/432 p/y (6 month) : 16/322 p/y (12 months) Advanced adenoma: 3/432 p/y (6 month) 7/322 p/y (12 months) Cancer: 1/432 p/y (6 months) : 0/322 p/y (12 months)	Any adenoma: 45/507 p/y (12 month) : 41/525 p/y (24 months) Advanced adenomas. 11/507 p/y (12 months) 12/525 p/y (24 months) Cancer: : 2/507 p/y (12 months) 4/525 p/y (24 months)			
Proximal adenoma at baseline						Any proximal disease vs distal: RR 2.00(CI95%1.36-2.92)		

CONCLUSIONS.

All the retrieved studies are concordant in concluding that there is a strong association between results of baseline screening colonoscopy and rate of serious incident lesions at follow up. All studies found that multiplicity, size, villousness, high degree dysplasia, proximal lesions at baseline are risk factors for any adenoma and advanced adenoma or cancer recurrence at follow up also if the studies used different ways to categorize patients on the basis of risk factors. Laiyemo found that only the villous component was an independent predictor of advanced adenoma recurrence at 4 years. Moreover patients with proximal adenomas are at increased risk and the 2006 guidelines (1) do not make any surveillance recommendations based on adenoma location at baseline. Authors of this study concluded that their study suggests that the adenoma based risk stratification used in the surveillance recommended by the 2006 guideline has limited predictability of advanced adenoma recurrence. On the other hand authors of the most recent meta-analysis of 8 trials (37) concluded that data of their meta-analysis showed relatively good discrimination between low and high-risk groups using current risk-stratification guidelines (1). Thus, their results strengthen the concept of risk stratification and should lead to improved physician compliance with these guidelines.

One prospective study found that the metachronous adenomas of all generations of recurrence were significantly smaller than the initial lesions (p<0.0001). In comparison with the initial lesion, the adenomas of the second (p=0.0003), third (p=0.002), and fourth generation (p=0.007) were significantly more often classified as tubular adenomas. In the first recurrence, exclusively low-grade dysplasia was found significantly more often (p<0.00001). In comparison with the initial lesion, the second generation also showed a significantly (p<0.0001) less high-grade dysplasia. During surveillance, high-grade dysplasia was a rare event. The first metachronous adenomas are significantly more often not advanced lesions compared with the initial findings (p<0.0001). In comparison with the initial lesion, the adenomas of the second (p<0.0001), third (p<0.0001), and fourth generation (p<0.0001) were also significantly more often classified as not advanced adenomas (LEVEL OF EVIDENCE III).

In the case control study, subjects with a history of advanced adenoma removed up to 10 yr earlier had an about 50% lower risk of CRC than subjects without previous large bowel endoscopy (OR: 0.50 CI95% 0.23–1.12). The risk reduction is particularly high in the first 5 year after advanced adenoma removal (after 5 years: OR 0.27 (0.10–0.77) and becomes non significant after 6-10 years follow up (OR: 2.09 CI95% 0.41–10.69). Subjects with a history of a non advanced adenoma removed up to ten years ago had an about 65% lower risk of CRC than subjects without previous large bowel endoscopy (OR: 0.36 CI95% 0.18–0.76)). The risk reduction is particularly high in the first 5 year after advanced adenoma removal (after 5 years: OR 0.14 CI95% 0.05–0.43) and becomes non significant after 6-10 years follow up (OR: 1.76 CI95% 0.45–6.85) (LEVEL OF EVIDENCE IV).

9.5.2 Evidence tables (see 9.8.2)

9.6 Optimal time interval between surveillance colonoscopies

9.6.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 6

What is the optimal time interval between surveillance colonoscopies?

PICOS

P: All patients with endoscopic removal of adenomas
I: Colonoscopy
C: Different time interval between surveillance colonoscopy
O: Rate of neoplasia
S: Observational study, RCT

RESULTS

We retrieved 3 clinical guidelines (1,3, 15) and 1 study reporting the results of 3 RCTs related to question 6 (10). The study reported the results of three RCTs which assessed the adenoma, advanced adenoma and cancer incidence /recurrence in people randomised to different follow up schedules and with different type of adenoma removed at index colonoscopy (10). The results of the study are reported in the table below. Authors concluded that 2-year intervals should be used between colonoscopies for patients with previous peduncolated adenomas and small flat and sessile adenomas, whereas larger flat and sessile adenomas may need intervals of 1 year.

	Kronborg 2006 study 1	Kronborg 2006 study 2	Kronborg 2006 study 3
Participants	671 patients with peduncolated or small, flat and sessile adenomas up to 5 mm tubular or tubulovillous adenomas	73 patients with flat and sessile adenomas more than 5 mm and villous adenomas	200 patients with flat and sessile adenomas more than 5 mm and villous adenomas
Follow up	Up to 20 years. Colonoscopy every 24 or 48 months	Up to 14 years. Colonoscopy every 6 or 12 months	Up to 20 years . colonoscopy every 1 or 24 months
RR of adenoma recurrence	48 vs 24 months: 0.88 (CI95%0.69-1.12)	12 vs 6 months: 0.82 (CI95%0.43-1.52)	24 vs 12 months: 0.88 (CI95%0.57-1.34)
RR of advanced adenoma recurrence	48 vs 24 months 1.15 (CI95%0.61-2.15)	12 vs 6 months :3.12 (CI95%0.47-14.50)	24 vs 12 months: 0.97 (CI95%0.40-2.35
RR of cancer incidence	48 vs 24 months 6.22 (CI95% 1.06-117.48)	12 vs 6 months Not evaluable because no cancer were seen in the 12 months interval	24 vs 12 months: 1.93 (CI95% 0.38-13.94)

One guideline (15) has been published in 2002 by the British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) and considered relevant literature published until 2000. It states that risk of patients should be stratified according to findings at baseline and suggest the following group and surveillance strategies.

Low risk: Patients with only 1–2, small (<1 cm) adenomas.
Recommendation: no follow up or five yearly until one negative examination.

Intermediate risk: Patients with 3–4 small adenomas or at least one >1 cm
Recommendation: three yearly until two consecutive negative examinations.

High risk: If either of the following are detected at any single examination (at baseline or follow up): >5 adenomas or >3 adenomas at least one of which is >1 cm.
Recommendation: An extra examination should be undertaken at 12 months before returning to three yearly surveillance

The second retrieved guideline (1) has been published in 2006 by the US Multi-Society Task Force and the American Cancer Society and considered relevant literature published until 2005. It states that risk of patients should be stratified according to findings at baseline and suggests the following group and surveillance strategies:

1.: Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years;

2. Patients with only 1 or 2 small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5–10 years

3. Patients with 3 to 10 adenomas, or any adenoma >1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years

4. Patients who have more than 10 adenomas at 1 examination should be examined at a shorter (<3 years) interval

5. Patients with sessile adenomas should be considered for follow-up evaluation at short intervals (2–6 mo) to verify complete removal; once complete removal has been established, subsequent surveillance needs to be individualised based on the endoscopist's judgment; completeness of removal should be based on both endoscopic and pathologic assessments.

The update of the joint guideline from the American Cancer Society, the Multy Society Task Force on colorectal cancer and the American College of radiology published in 2008 (3) did not consider reviewed recent literature on CRC screening and surveillance for individual at increased risk, as people with a personal history of adenomatous polyps or CRC. For these populations it reported the recommendations made in 2006 .

CONCLUSIONS

The two retrieved guidelines are of good methodological quality because they reported the method used to search the evidence and to analyse and synthesise the evidence and to reach the consensus among the panellist. One guideline (1) does not use a grading system but reported the results of primary studies, the other (15) used a grading of the strength of the recommendation which is related to the level of evidence. Both the guidelines are concordant in defining low risk people as ones with 1 or 2 small (<1 cm) tubular adenomas with only low-grade dysplasia; one guideline suggests for these people no screening or 5 years screening, the other suggest 5-10 years interval screening. The intermediate risk group is defined differently by the two guidelines: one consider people with 3-4 small adenomas or at least one >1 cm, while the other consider people with 3 to 10 adenomas or any adenoma >1 cm, or any adenoma with villous features, or high-grade dysplasia. Both guidelines recommend screening at 3 years interval for this group. The high risk group is also defined differently:

one guideline considers people with more than 5 adenomas or more than 3 adenomas and at least one of which is >1 cm, while the other guideline consider people with more than 10 adenomas. The first guideline recommends screening at a 1-year interval before returning to 3-yearly surveillance, while the other suggests a screening interval less than 3 years without any further specification. The second guideline considers people with sessile adenomas separately and recommends screening for this group after a 2-6 month interval to verify complete removal, and then based on the endoscopist's judgment. (LEVEL OF EVIDENCE III)

9.6.2 Evidence tables (see 9.8.2)

9.7 Risk of neoplasia after local removal of a low-risk pT1 cancer

9.7.1 Summary document

Silvia Minozzi

CLINICAL QUESTION 7

What is the risk of neoplasia after local removal of a low-risk malignant polyp (T1 –carcinoma)?

PICOS

P: All patients with removal of a low-risk T1- cancer
I: colonoscopy,
C: Not applicable
O: Rate of neoplasia
S: Observational study

RESULTS

We retrieved 4 studies (4,5,7,8,) relating to question 7. One is a systematic review and clinical guideline (4) which included 23 RCTs or prospective studies on colonoscopy performed in patients with resected CRC published 1966 to January 2005. Two are prospective cohort studies (7, 8), one is a retrospective cohort study (5).

The systematic review and clinical guidelines found that in 0.6% of patients a metachronous cancer was detected at surveillance colonoscopy within 24 months.

Primary studies

	Di Gregorio 2005	Lieberman 2007	Chu 2003
Participants	145 patients with T1 stage CRC	81 participants with invasive cancer or adenoma with high	192 patients with colorectal cancer stage 0 (5%),I

		grade dysplasia at baseline colonoscopy	(52%),II(43%), Cancer confined to polyps (24%).
Follow up	5 years	5.5 years	3 years
Risk of adenoma			Stage I: 24%
Risk of advanced neoplasia		CR:34.8% RR vs no neoplasia: 13.56	
Recurrence of cancer	2.8%		

CONCLUSIONS

The results of primary studies are difficult to summarise because they consider patients with different baseline characteristics and different outcomes.

The guideline recommended that patients with curative endoscopic resection of stage I colon cancer are candidates for surveillance colonoscopy as patients with surgical resection of stage I,II or III colon and rectal cancer. Patients undergoing curative resection should undergo a colonoscopy 1 year after the resection. If the examination performed after 1 year is normal, the interval before the next subsequent colonoscopy should be 3 years. If the examination after 3 year is normal, the next subsequent examination should be performed after 5 years. (LEVEL OF EVIDENCE III)

9.7.2   Evidence tables (see 9.8.2)

9.8   Quality indicators and standards

9.8.1   Summary document

Silvia Minozzi

CLINICAL QUESTION 8

Which are appropriate quality indicators and standards to evaluate surveillance after polypectomy?

PICOS

P: All patients with removal of adenomas
I: Quality indicators of surveillance (colonoscopy)
C: Not applicable
O: Safety, optimal use of endoscopic resources, yield of neoplasia detection
S: Observational studies

RESULTS

We retrieved 1 guideline related to question 8. It is the Guideline of the American Society of Gastro-intestinal Endoscopy (ASGE) published in 2006 (12). It could be considered a guideline of intermediate methodological quality because it does not report any information about the method of retrieving studies or collecting and analysing the evidence but it uses a grading of strength of recommendation which is related to the level of evidence retrieved, The guideline refers to quality indicators for all the aspects related to colonoscopy and not only for surveillance after polypectomy. The quality indicators listed in the guideline for surveillance are the following:

1. Appropriate indication (1CC_Strong recommendation; can apply to most practice settings in most situations)

2. Informed consent is obtained, including specific discussion of risks associated with colonoscopy (3: Weak recommendation; likely to change as data become available_)

3. Use of recommended postpolypectomy and postcancer resection surveillance intervals (1A_Strong recommendation; can be applied to most clinical settings)

5. Documentation in the procedure note of the quality of the preparation (2C)

6. Caecal intubation rates (visualisation of the cecum by notation of landmarks and photo documentation of landmarks should be present in every procedure) (1C)

7. Detection of adenomas in asymptomatic individuals (screening) (1C)

11. Mucosally based pedunculated polyps and sessile polyps >2 cm in size should be endoscopically

resected or documentation of unresectabiltiy obtained (3)

12. Incidence of perforation by procedure type (all indications vs screening) is measured (2C)

13. Incidence of postpolypectomy bleeding is measured (2C)

14. Postpolypectomy bleeding managed nonoperatively (1C)

The authors of the guideline underline that this list of potential quality indicators was meant to be a comprehensive listing of measurable end points. It is not the intention of the task force that all end points be measured in every practice setting. In most cases, validation may be required before a given end point may be universally adopted

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9.8.2 Evidence tables

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Conclusions and recommendations
Winawer 2006 Guideline of US Multi-society Task Force and the American Cancer Society	Colonoscopy surveillance after polypectomy	Systematic review and clinical guideline Medline search 1990-2005, reference of retrieved articles	15 prospective studies on colonoscopy or sigmoidodcopy assessing the relationship between baseline examination findings and the detection of any adenoma during follow up of at least 10 years	Incidence of any adenoma at follow up Incidence of advanced adenoma (≥ 1 cm, any villous component, high grade dysplasia or invasive cancer) at follow up	**Risk factors for any adenoma** Multiple adenoma(≥ 3): multiplicity at baseline predict subsequent detection of adenoma (4 RCTs, 3 observational studies) Adenoma size(>1 cm) : adenoma >1 cm predict subsequent detection of adenoma (4 RCTs, 5 observational studies) Tubulovillous histology Predict the subsequent detection of adenomas (3 RCTs, 4 observational studies) High grade dysplasia predict the subsequent detection of adenomas (2 (RCTs, 3 observational studies) Proximal adenomas predict the detection of subsequent adenomas (2 RCTs, 2 observational studies) **Risk factor for advanced adenomas** Multiple adenoma(≥ 3): predict subsequent detection of advanced adenoma (4 RCTs, 8 observational studies) Adenoma size(>1 cm) : adenoma >1 cm predict subsequent detection of advanced adenoma (3 RCTs, 11 observational studies) Tubulovillous histology Predict the subsequent detection of advanced adenomas (3 RCTs, 12 observational studies) High grade dyplasia predict the subsequent detection of advanced adenomas (2 (RCTs, 8 observational studies) Proximal adenomas predict the detection of subsequent advanced adenomas (2 RCTs, 4 observationals studies)	**III** The most consistent evidence for predicting subsequent advanced adenomas indicates that multiplicity, size, villous histology, and high-grade dysplasia are the important factors at baseline. Based on these factors, patients can be stratified at the time of colonoscopy into lower or higher risk for subsequent advanced adenomas. 1. Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years; an exception is patients with a hyperplastic polyposis syndrome; they are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up evaluation 2. Patients with only 1 or 2 small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5–10 years; the precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician) 3. Patients with 3 to 10 adenomas, or any adenoma >1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years providing that

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Conclusions and recommendations
						piecemeal removal has not been performed and the adenoma(s) are removed completely; if the follow-upcolonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years 4. Patients who have more than 10 adenomas at 1 examination should be examined at a shorter (<3 y) interval, established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome 5. Patients with sessile adenomas that are removed piecemeal should be considered for follow-up evaluation at short intervals (2–6 mo) to verify complete removal; once complete removal has been established, subsequent surveillance needs to be individualised based on the endoscopist's judgment; completeness of removal should be based on both endoscopic and pathologic assessments

Quality assessment: Description of the clinical specialisation of the members of the panel author of the guideline: NO; search strategy described (databases, years covered, any language restriction): YES; inclusion criteria of primary studies stated: YES; method used to analyse and synthesise the evidence and to reach the consensus among the panellist to elaborate the recommendation described: YES; presence of a grading of level of evidence and/or of the strength of the recommendation: NO; presence of a complete reference list :YES; detailed description of study results: YES.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Saini 2006	Colonoscopy surveillance after polypectomy	Systematic review Medline, Embase 1980-January 2003	15 prospective studies on colonoscopy or sigmoidodcopy assessing the relationship between baseline examination findings and the detection of any adenoma during follow up	Incidence of advanced adenoma (≥ 1 cm, any villous component, high grade dysplasia or invasive cancer) at follow up	**Risk factor for advanced adenomas** Multiple adenoma (>3 vs 1-2) : RR 2.52 (CI95% 1.07-5.97 (4 studies) Adenoma size (≥ 1 cm vs <1cm) RR: 1.39 (CI 95% 0.86-2.26) (4 studies) Tubulovillous histology vs tubular : RR : 1.26 (CI95% 0.95-1.66)(3 studies) High grade dysplasia vs no : RR: 1.84 (CI95% 1.06-3.19) (2 studies) Proximal adenomas is a risk factor for advanced adenomas (2 RCTs, 4 observational studies) **Risk factors for any adenoma** Multiplicity, size, age, tuvulovillous/villous histology, dysplasia, advanced adenoma, adenoma in the proximal colon (14 studies, meta-analysis not performed)	III

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Conclusions and recommendations
Rex 2006 Guideline of US Multi-society Task Force and the American Cancer Society	Colonoscopy surveillance after cancer resection	Systematic review and clinical guideline Medline search 1966-january 2005, Cochrane databases of systematic review and DARE 2004, Issue 4, reference of retrieved articles	23 RCTs or prospective studies on colonoscopy performed in patients with resected CRC to detect recurrent or metachronus neoplasms	Metachronous cancer detected at perioperative clearing colonoscopy or at surveillance colonoscopy	Patients with metachronous cancer detected at perioperative clearing colonoscopy: 137/9029 (1.5% Patients with metachronous cancer detected at surveillance colonoscopy within 24 months: 57/9029 (0.6%)	**III** These findings were considered sufficient to warrant a colonoscopy 1 year after resection or after perioperative clearing colonoscopy Patients with curative endoscopic resection of stage I colon cancer are candidates for surveillance colonoscopy as patients with surgical resection of stage I,II or III colon and rectal cancer Patients with colon and rectal cancer should undergo high quality perioperative clearing by preoperative colonoscopy in case of nonobstructing colon cancer. In case of obstructing colon cancer CT colonography with intravenous contract or double contrast barium enema could be used. In these cases a colonoscopy to clear the colon for sinchronous disease should be considered 3-6 months after the resection if no unresectable metastasis are found. Patients undergoing curative resection should undergo a colonoscopy 1 year after the resection. If the examination performed 1 year after is normal, the interval before the next subsequent colonoscopy should be of 3 years If the examination after 3 year is normal, the next subsequent examination should be performed after 5 year

Quality assessment: Description of the clinical specialisation of the members of the panel author of the guideline: NO; search strategy described (databases, years covered, any language restriction): YES; inclusion criteria of primary studies stated: YES; method used to analyse and synthesise the evidence and to reach the consensus among the panellist to elaborate the recommendation described: YES; presence of a grading of level of evidence and/or of the strength of the recommendation: NO; presence of a complete reference list :YES; detailed description of study results: NO.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Di Gregorio 2005	Retrospective cohort study using the Colorectal Cancer registry data of 16 health care district of the region Emilia Romagna, Italy	150 patients with T2 stage CRC 145 patients with T1 stage CRC	5 years survival Recurrence rate	5 years	5 years survivals Stage T1: 82.1% Stage T2: 80% Recurrence rate: Stage T1: 2.8% Stage T2: 10.7%	III

Quality assessment: Population truly representative of the population with CRC; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Complete follow up for all subjects

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Le Bodic 2003	Retrospective cohort study using the Colorectal Cancer registry data of Loire-Atlantique Regione, France	2,604 patients with a first adenoma removed	Recurrence of colorectal neoplasia Incidence of severe lesions	28 months (average)	Patients with new neoplastic lesions: 28.3% New severe lesions (high grade dysplasia or cancer) in people with initial adenomas <5 mm: 1.5% 5-20 mm: 3% >20 mm: 7% New severe lesions (high grade dysplasia or cancer) in people with initial adenoma with high degree dysplasia: 4.2% Low grade dysplasia: 2.2%	III

Quality assessm ent: Population truly representative of the population with adenomas; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Complete follow up for all subjects.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Lieberman 2007	Prospective cohort study USA	1,672 patients with baseline colonoscopy (501 without neoplasia and 1171 with neoplasia, 81 of which with invasive cancer or adenoma with high grade dysplasia	Incidence of neoplasia at follow up examinations basing on baseline findings	5.5 years	Timing of colonoscopy: n. of advanced neoplasia at 1-3 years follow up No neoplasia at baseline: 0 Tub ad <1 cm: 4.5% Tub ad >1 cm: 8.8% Villous: 13.1% HGD: 12.2% Cancer: 27.3% 3-5 years follow up No neoplasia at baseline: 2.1% Tub ad <1 cm: 5.8% Tub ad >1 cm: 0% Villous: 10% HGD: 0% Cancer: 0% Cumulative risk of advanced neoplasia No neoplasia at baseline: 2.4% Tub ad <1 cm: 6.1% Tub ad >1 cm: 15.5% Villous: 16.1% HGD: 17.4% Cancer: 34.8% 1-2 adenomas: 6.5% 3-4 adenomas: 15.9% 5-9 adenomas: 17.2% 10 +: 12.5% RR of advanced neoplasia basing on baseline findings No neoplasia at baseline: 1 Tub ad <1 cm: 2.56 Tub ad> 1 cm: 6.4 Villous: 6.5 HGD: 6.87 Cancer: 13.56	III There is a strong association between results of baseline screening colonoscopy and rate of serious incident lesions during 5.5 years follow up. Patients with 1-2 tubular adenomas less than 1 cm represent a low risk group.

Quality assessment: Population truly representative of the population at average risk; Non exposed cohort drawn form the same community as the exposed cohort; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; subjects lost to follow 28.6%; description provided of those lost.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Chu 2003	Prospective cohort study of patients included in the randomised controlled trial Sothwest Oncology Group 9041 Calcium chemoprevention trial USA	192 patients with colorectal cancer stage 0 (5%),I (52%),II(43%), Cancer confined to polyps (24%). Not specified how many patients had an endoscopical removal of cancer	Incidence of neoplasia at follow up examinations basing on baseline findings	3 years	Overall neoplasia recurrence rate: 31% Adenoma recurrence rate by stage Stage 0: 37% Stage I: 24% Stage II: 39% There were not a statistically significant difference in adenoma recurrence rate when analysed by sex, age, site or whether the cancer was confined to a polyp	III

Quality assessment: Population truly representative of the population at average risk; Non exposed cohort drawn form the same community as the exposed cohort; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; subjects lost to follow 12.8%; description provided of those los

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Neugut 1995	Prospective cohort USA	807 patients who had repeated colonoscopy at three colonoscopy practice in New York 508 with normal results at index colonoscopy 299 with adenoma at index colonoscopy USA	Adenoma incidence Adenoma recurrence	3 years	Patients without adenoma at index colonoscopy who repeated colonoscopy 99 (19.4%) Patients with adenoma who repeated colonoscopy: 178 (59.5%) Adenoma incidence: 24/99 (24%) Adenoma recurrence: 81/178 (46%)	III The most limitation of this study is the low percentage of people who underwent repeated colonoscopy and the selection of patients who repeated colonoscopy who are probably not representative of the entire population

Quality assessment: Population truly representative of the population at average risk; Non exposed cohort drawn from the same community as the exposed cohort; Cohort with and without adenoma at index colonoscopy comparable for major prognostic factor; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Only 99 (19.4%) of patients without adenoma at index colonoscopy and 178 (59.5%) of patients with adenoma repeated colonoscopy.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Kronborg 2006	Three RCTs Study 1 Participants randomised to 24 or 48 months intervals between surveillance examination Study 2 Participants randomised to 6 or 12 months intervals between surveillance examination Study 3 Participants randomised to 12 or 24 months intervals between surveillance examination	Study 1 671 patients with peduncolated or small, flat and sessile adenomas up to 5 mm tubular or tubulovillous adenomas Study 2 73 patients with flat and sessile adenomas more than 5 mm and villous adenomas Study 3 200 patients with flat and sessile adenomas more than 5 mm and villous adenomas Denmark	Adenoma Recurrence Advanced adenoma recurrence	Up to 20 years in studies 1 and 3, up to 14 years in study 2	**Study 1** <u>Cumulated recurrence of adenoma</u>: 24 month intervals: 145/3000 person/year of observation 48 months interval: 123/2894 person/year of observation <u>Cumulated risk of advanced adenoma</u> 24 month intervals: 22/3000 person/year of observation 48 months interval: 24/2894 person/year of observation <u>Cumulated risk of cancer</u> 24 month intervals: 1/3000 person/year of observation 48 months interval: 6/2894 person/year of observation <u>RR of new adenoma</u> (48 vs 24 months): 0.88 (CI95%0.69-1.12) <u>RR of new advanced adenoma</u>: 1.15 (CI95%0.61-2.15) <u>RR of cancer</u>: 6.22 (CI95% 1.06-117.48) **Study 2** <u>Cumulated incidence of adenoma</u>: 6 month intervals: 26/432 person/year of observation 12 months interval: 16/322 person/year of observation <u>Cumulated risk of advanced adenoma</u>: 6 month intervals: 3/432 person/year of observation 12 months interval: 7/322 person/year of observation <u>Cumulated risk cancer</u>: 6 month intervals: 1/432 person/year of observation 12 months interval: 0/322 person/year of observation <u>RR of new adenoma</u> (12 vs 6 months): 0.82 (CI95%0.43-1.52) <u>RR of new advanced adenoma</u>: 3.12 (CI95%0.47-14.50) **Study 3** <u>Cumulated incidence of adenoma</u>: 12 month intervals: 45/507 person/year of observation 24 months interval: 41/525 person/year of observation <u>Cumulated risk of advanced adenoma</u>: 12 month intervals: 11/507 person/year of observation 24 months interval: 12/525 person/year of observation	**II** 2 years intervals should be used between colonoscopies for patients with previous peduncolated adenomas and small flat and sessile adenomas, whereas larger, flat and sessile adenomas may need intervals of 1 year.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
					<u>Cumulated risk of cancer:</u> 12 month intervals: 2/507 person/year of observation 24 months interval: 4/525 person/year of observation <u>RR of new adenoma</u> (24 vs 12 months): 0.88 (CI95%0.57-1.34) <u>RR of new advanced adenoma</u>: 0.97 (CI95%0.40-2.35) <u>RR of cancer</u>: 1.93 (CI95% 0.38-13.94)	

Quality assessment: avoidance of selection bias: unclear allocation concealment; performance bias: not applicable; protection against contamination: not specified; attrition bias: number of patients at risk for years of observation reported; detection bias: blinding of outcome assessor: nor relevant because the outcome measure are objectives.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Laiyemo 2008	Analysis of prospective data from the Polyp Prevention Trial USA	1,905 patients who had an adenoma removed at baseline and completed the trial. Both experimental and control subjects included because the dietary intervention had no effect on adenoma recurrence	Non advanced adenoma recurrence Advanced Adenoma recurrence	4 years	Subjects with non advanced adenoma recurrence: 33% Subjects with advanced adenoma recurrence: 6.6% Advanced adenoma recurrence in patients considered at high risk according to the 2006 guidelines (3 or more adenomas or adenoma >1 cm or with villous histology or with high grade dysplasia) : 0.09 (CI95% 0.07-0.11) Advanced adenoma recurrence in patients considered at low risk by the guideline: 0.05 (CI95%0.04-0.06) Multivariate analysis of predictor of advanced adenoma recurrence with all adenoma characteristic in the model: Any proximal disease vs distal: RR 2.00(CI95%1.36-2.92) Villous component vs no villous component: RR2.25 (CI95%1.49-3.39) High grade dysplasia vs no: RR1.11 (CI95%0.64-1.90) Size >1 cm vs <1cm: RR0.93 (CI95%0.61-1.41) ≥3 adenomas vs less: RR1.46 (CI95%0.96-2.2)	**III** Only the villous component was an independent predictor of advanced adenoma recurrence at 4 years. Moreover patients with proximal adenomas are at increased risk and the guideline do not make any surveillance recommendations based on adenoma location at baseline. Authors concluded that their study suggests that the adenoma based risk stratification used in the surveillance recommended by the 2006 guideline has limited predictability of advanced adenoma recurrence

Quality assessment: Population truly representative of the population at average risk; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; 8.4% of subjects lost at follow up.

Author, publication year	Intervention	Study design	Participants	grading	Conclusions and recommendations
Rex 2006 Guideline of American Society of gastrointestinal Endoscopy (ASGE)	Quality indicator for colonoscopy	clinical guideline	Number of studies retrieved not specified	**Grade of recommendation** **1A** Clear Randomised trials without important limitations Strong recommendation; can be applied to most clinical settings **1B** Clear Randomised trials with important limitations (inconsistent results, nonfatal methodologic flaws) Strong recommendation; likely to apply to most practice settings **1CC** Clear Overwhelming evidence from observational studies Strong recommendation; can apply to most practice settings in most situations **1C** Clear Observational studies Intermediate-strength recommendation; may change when stronger evidence is available **2A** Unclear Randomised trials without important limitations Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values **2B** Unclear Randomised trials with important limitations (inconsistent results, nonfatal methodologic flaws) Weak recommendation; alternative approaches may be better under some circumstances **2C** Unclear Observational studies Very weak recommendation; alternative approaches likely to be better under some circumstances **3** Unclear Expert opinion only Weak recommendation; likely to change as data become available	**Colonoscopy indications**: After adequate clearance of neoplastic polyp(s) survey at 3- to 5-year intervals **Indications for colonoscopy and appropriate intervals*** Postadenoma resection 1-2 tubular adenomas of /1 cm : 5-10 years 3-10 adenomas or adenoma with villous features, ≥1 cm or with HGD: 3 years >10 adenomas: <3 years Sessile adenoma of ≥2 cm, removed piecemeal: 2-6 months Postcancer resection Clear colon, then in 1 year, then 3 year, then 5 year **Summary of Quality indicators** 1. Appropriate indication (1CC) 2. Informed consent is obtained, including specific discussion of risks associated with colonoscopy (3) 3. Use of recommended postpolypectomy and postcancer resection surveillance intervals (1A) 4. Use of recommended ulcerative colitis/Crohn's disease surveillance intervals (2C) 5. Documentation in the procedure note of the quality of the preparation (2C) 6. Caecal intubation rates (visualisation of the cecum by notation of landmarks and photo documentation of landmarks should be present in every procedure) (1C) 7. Detection of adenomas in asymptomatic individuals (screening) (1C) 8. Withdrawal time: mean withdrawal time should be /R6 minutes in colonoscopies with normal results performed in patients with intact anatomy

Author, publication year	Intervention	Study design	Participants	grading	Conclusions and recommendations
					(2C) 9. Biopsy specimens obtained in patients with chronic diarrhea (2C) 10. Number and distribution of biopsy samples in ulcerative colitis and Crohn's colitis surveillance. Goal: 4 per 10-cm section of involved colon or approximately 32 specimens per case of pancolitis (1C) 11. Mucosally based pedunculated polyps and sessile polyps !2 cm in size should be endoscopically resected or documentation of unresectabiltiy obtained (3) 12. Incidence of perforation by procedure type (all indications vs screening) is measured (2C) 13. Incidence of postpolypectomy bleeding is measured (2C) 14. Postpolypectomy bleeding managed nonoperatively (1C) *This list of potential quality indicators was meant to be a comprehensive listing of measurable end points. It is not the intention of the task force that all end points be measured in every practice setting. In most cases, validation may be required before a given end point may be universally adopted.

Quality assessment: Description of the clinical specialisation of the members of the panel author of the guideline: YES; search strategy described (databases, years covered, any language restriction): NO; inclusion criteria of primary studies stated: NO; method used to analyse and synthesise the evidence and to reach the consensus among the panellist to elaborate the recommendation described: NO; presence of a grading of level of evidence and/or of the strength of the recommendation: YES; presence of a complete reference list :YES; detailed description of study results: YES.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Schoen 2003	Colonoscopy surveillance after positive and negative colonoscopy	Narrative review	4 studies. considered only the studies with results relating the incidence of adenomas after a negative colonoscopy, because for other questions there are studies of better methodological quality	Incidence of adenoma and advanced adenomas after a negative colonoscopy	Neugut 1995: 99 subjects; follow up:5.4 years; Adenoma incidence: 24%; advanced adenoma incidence: not reported Rex 1996: 154 subjects; follow up: 5.6 years Adenoma incidence: 27% Advanced adenoma incidence: 0% Squillace 1994: 29 subjects; follow up: 5.7 years: Adenoma incidence: 41.4% Advanced adenoma incidence: 3.4% Hixon 1994: 58 subjects; follow up: 2 years: Adenoma incidence: 52% Advanced adenoma incidence: 10% (the study included also subjects with adenoma/carcinoma at baseline)	**III** The author of the review underlines that the study populations of the studies considered are not representative of the general population, are dominated by men and follow up is variable

Quality assessment: bibliographic search, years covered by the search, inclusion and exclusion criteria of primary studies not reported; results of studies reported narratively, only for some of them reported the results.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Yamaji 2004	Prospective cohort study Japan	6,225 asymptomatic subjects participating in an annual colonoscopic screening program and completing three or more colonoscopies	Incidence of neoplasia at follow up examinations basing on baseline findings. Recurrence of any neoplasia	3 years	Subjects with no neoplasms at the initials two colonoscopies: 4084 Incidence of any type of neoplasia: 848/4084 (20.8%) Estimated annual incidence rate: 7.2% Incidence of advanced adenoma: 30/4084 (0.73%) Estimated annual incidence rate: 0.21% Estimated annual incidence rate stratified for sex and age of any neoplasia: Female <40 : 3.1% (CI95% 1.3-6.3) Female 40-49: 3.2% (CI95%2.4-4.2) Female 50-59: 6.7% (CI95% 5.4-8.4) Female>60: 7.3% (CI95%4.5-11.3) Male <40: 4.7% (CI95%3.9-5.9) Male 40-49: 8.2% (CI95%7.5-9.2) Male 50-59: 10.1% (CI95%9.0-11.7) Male>60: 11.4% (CI95%9.1-14.2) Subjects with adenoma removed at baseline. 2141 Recurrence of any neoplasia::659/2141 (30.8%)	III The incidence rate in subjects with no neoplastic lesions is quite high.

Quality assessment: Population truly representative of the population at average risk; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Only 6225 out of 68053 who were first screened had at least three colonoscopies.

Author, publication year	Intervention	Study design	Participants	grading	Conclusions and recommendations
Atkin 2002 Guideline of the British Society of Gastroenterology (BSG) and the Association of Coloproctolgy for Great Britain and Ireland (ACPGBI))	Surveillance after removal of adenomatous polyps	Clinical guideline	Number of studies retrieved not specified.	**Categories of evidence** Ia: Evidence obtained from meta-analysis of randomised controlled trials. Ib: Evidence obtained from at least one randomised controlled trial. IIa: Evidence obtained from at least one well designed controlled study without randomisation. IIb: Evidence obtained from at least one other type of well designed quasi-experimental study. III: Evidence obtained from a well designed nonexperimental descriptive study, such as comparative studies, correlation studies, and case studies. IV: Evidence obtained from expert committee reports or opinions or clinical experiences of respected authorities. The evidence category is indicated in parentheses within the reference section. **Grading of recommendations** The strength of each recommendation is dependent upon the category of the evidence supporting it, and is graded according to the following system. A: Evidence categories Ia and Ib. B: Evidence categories IIa, IIb, III. C: Evidence category IV.	**Risk of colorectal cancer and adenomas with advanced** **pathology (>1 cm or severely dysplastic)** Risk can be stratified according to findings at baseline and refined at each subsequent surveillance examination. (Recommendation Grade B**)** **Low risk** Patients with only 1–2, small (<1 cm) adenomas. *Recommendation: no follow up or five yearly until one negative examination.* **Intermediate risk** Patients with 3–4 small adenomas or at least one >1 cm *Recommendation: three yearly until two consecutive negative examinations.* **High risk** If either of the following are detected at any single examination (at baseline or follow up): >5 adenomas or >3 adenomas at least one of which is >1 cm. *Recommendation: An extra examination should be undertaken at 12 months before returning to three yearly surveillance* **Stopping surveillance due to comorbidity or age** The cut off age for stopping surveillance is usually 75 years, but should also depend upon patient wishes and comorbidity. (Recommendation Grade C)

Quality assessment: Description of the clinical specialisation of the members of the panel author of the guideline: YES; search strategy described (databases, years covered, any language restriction): YES; inclusion criteria of primary studies stated: NO; method used to analyse and synthesize the evidence and to reach the consensus among the panellist to elaborate the recommendation described: YES; presence of a grading of level of evidence and/or of the strength of the recommendation: YES; presence of a complete reference list :YES; detailed description of study results: YES.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Bonithon-Kopp 2004	Prospective cohort data drawn from European Fiber calcium Intervention Trial RCT UK	552 participants who had adenoma removed at baseline and who completed the 3 years study.	Recurrence of any adenoma	3 years	Recurrence of any adenoma: 122/552 (22.1%) Recurrence of advanced adenoma. 41/552 (7.4%)	III

Quality assessment: Population truly representative of the population with adenomas; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Lost at follow up 14%.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Lund 2001	Prospective cohort data drawn from an RCT on different screening surveillance protocols UK	776 participants who had adenoma removed at baseline.	Recurrence of any adenoma	11 years	Recurrence of any adenoma: 81/776 (26%) Cancer incidence: 4/776 (0.5%)	III

Quality assessment: Population truly representative of the population with adenomas; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Lost at follow up not clearly reported.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Martinez 2001	Prospective cohort data drawn form the weat bran fiber RCT because the intervention had no significant effect on adenoma recurrence USA	1287 participants who had at least one colonoscopy and had data on baseline characteristics of adenoma.	Recurrence of any adenoma Advanced adenoma recurrence	3 years	Recurrence of any adenoma: 625/ 1287 (48.6%) Advanced adenoma recurrence:146/1287 11.3%	**III**

Quality assessment: Population truly representative of the population with adenomas; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Complete follow up for all subjects.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Huang 2001	Retrospective cohort study USA	404 patients with baseline colonoscopy (362 without neoplasia and 41 with hyperplastic polyps at baseline colonoscopy	Incidence of adenoma at follow up examinations basing on baseline findings	4.3 years	Incidence of adenoma Hyperplastic polyps at baseline: 18/41 (43% Negative colonoscopy at baseline: 77/362 (21%)	**III** Patients found to have hyperplastic polyps at baseline may have twice the risk of adenomas on follow up as compared with those who have clean initial examinations.

Quality assessment: Population truly representative of the population at average risk; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; No subjects lost to follow.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Hooi 2001	Retrospective cohort study Australia	1,047 patients with normal baseline colonoscopy Data extracted from a multicenter endoscopic databases	Cancer incidence	5 years	Cancer incidence: 5/1047 (0.5%)	III

Quality assessment: Population truly representative of the population at average risk; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; No subjects lost to follow.

Author, publication year	Study design	Participants	Outcomes	Results	Level of evidence
Gorski1999	Retrospective study USA	29 patients operated for rectal cancer who had one or more negative colonoscopy before diagnosis	Stage of cancer. Interval between prior colonoscopy and diagnosis	Stage of cancer: Stage 0:7 Stage I: 10 Stage II: 8 Stage II: 4 Mean interval since prior colonoscopy in patients with poorly differentiated cancer: 26 months Mean interval since prior colonoscopy in patients with well or moderately differentiated cancer: 22 months	IV Size, differentiation and stage of colorectal cancer in addition to the interval to diagnosis suggest that the majority of cancers followed prior false negative examinations.

Author, publication year	Study design	Participants	intervention	Outcomes	Results	Level of evidence
Jahn 1992	Prospective cohort diagnostic accuracy study Denmark	529 patients with previous curative surgery for colorectal cancer. 279 patients with previous removal of adenomas	FOBT by Haemoccult II (three consecutive stool with dietary restriction and without rehydration) Reference standard: colonoscopy	Sensitivity of haemoccult II Characteristic of adenoma detected at colonoscopy	Sensitivity for local recurrence of cancer: 3/9(33.3%) Sensitivity for metachronus cancer 2/13 (15.4%) Sensitivity for adenomas. 31/186 (16.6%) Dukes A cancer: 11/13 (one positive at hemoccult) Bukes C: 2/13 (one positive for at hemoccult) Sensitivity for adenomas <10 mm: 8/95 (8.4%) Sensitivity for adenomas. 10-19 mm: 6/31(19.3%) Sensitivity for adenomas >20 mm. 4/10 (40%) Sensitivity for 1 adenoma: 18/136 (13.2%) Sensitivity for two or more adenomas: 13/50 (26%) Sensitivity for tubular adenomas. 18/152 (11.8%) Sensitivity for tubulovillous and villous adenomas: 13/34 (38.2%) Sensitivity for adenomas with mild dysplasia: 13/128 (10.1%) Sensitivity for adenoma with severe dysplasia. 18/58 (31%)	III The test was more sensitive with large and multiple adenomas, adenoma with villous component and severe dysplasia, but did not reach more than 40%. Authors concluded that markers more sensitive than Haemoccult II are needed to detect metachrouns cancers and new adenomas

Quality assessment: Prospective cohort study; Execution of the index test and of the reference test clearly described.; Index test and reference test interpretation without knowledge of the other test results. Characteristics of patients at baseline not clearly described (stage of cancer, characteristic of adenoma removed); All the patients received the reference standard test (avoidance of verification bias); Description of incomplete test reported.

Author, publication year	Study design	Participants	Intervention	Outcomes	Results	Level of evidence
Hall 1999	Prospective cohort diagnostic accuracy study UK	54 patients with previous curative surgery for colorectal cancer.	FOBT by Haemoccult (six specimen with dietary restriction. Reference standard: colonoscopy	Sensitivity and specificity of haemoccult	Sensitivity for neoplastic lesions: 0/4 (0%) Specificity: 37/38 (97.3%) 1 false positive hemoccult	**III** Haemoccult is an unreliable method of detecting metachronus lesions after curative colon resection: It is not even complementary to colonoscopy and should not used for this purpose

Quality assessment: Prospective cohort study; Execution of the index test and of the reference test clearly described.; Index test and reference test interpretation without knowledge of the other test results. Characteristics of patients at baseline clearly described (stage of cancer). All the patients received the reference standard test (avoidance of verification bias). Description of incomplete test reported.

Author, publication year	Study design	Participants	Intervention	Outcomes	Results	Level of evidence
Skaife 2003	Prospective cohort diagnostic accuracy study Singapore	611 patients with previous curative surgery for colorectal cancer.	Immunological FOBT Reference standard: colonoscopy	Sensitivity and specificity of immunological FOBT	Sensitivity for neoplastic lesions:21/59 (35.6%) Sensitivity for cancer: 9/9 (100%) Sensitivity for polyps: 12/50 (24%) Specificity: 524/557 (94%) 33 false positive	**III** The immunological FOBT provides sensitive detection of metachronus and recurrent cancer. Routine application may be used to reduce the frequency of colonoscopy as a negative FOBT may be taken as a sign that colonoscopy could be safely deferred.

Quality assessment: Prospective cohort study; Execution of the index test and of the reference test clearly described.; Not specified if the Index test and reference test were interpreted without knowledge of the other test results. Characteristics of patients at baseline clearly described (stage of cancer); All the patients received the reference standard test (avoidance of verification bias). Description of incomplete test reported.

Author, publication year	Study design	Participants	intervention	Outcomes	Results	Level of evidence
Nava 1982	Prospective cohort diagnostic accuracy study USA	240 patients with previous curative surgery for colorectal cancer.	Haemoccult II FOBT (two specimen without dietary restriction) Reference standard: colonoscopy	Sensitivity of FOBT	Sensitivity for neoplastic lesions: 12/65 (18.5%) Sensitivity for metachronus cancer: 3/9 (33%) Sensitivity for recurrent cancer: 7/14 (50%) Sensitivity for adenomas: 2/42 (18.5%)	**III** Many serious mucosal neoplasms would be missed if one relies heavily upon hemoccult testing

Quality assessment: Prospective cohort study; Execution of the index test and of the reference test clearly described.; Index test and reference test were interpreted without knowledge of the other test results. Characteristics of patients at baseline clearly described (stage of cancer). All the patients received the reference standard test (avoidance of verification bias).

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Nozaki 1997	Prospective cohort study Japan	6715 patients who had an adenoma removed at baseline	Non advanced adenoma recurrence Advanced Adenoma recurrence Cancer incidence	6 years	Cancer incidence: 31/6715 (0.63%); Any adenoma recurrence: 2967/6715 (44.2%) Adenoma with high grade dysplasia incidence: 38/6715 (0.7%)	**III**

Quality assessment: Population truly representative of the population at average risk; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; No subjects lost at follow up.

Author, publication year	Intervention	Study design	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Singh 2006	All individuals who had undergone colonoscopy or sigmoidoscopy in Manitoba between April, 1984 and December 2003 and had negative results	Population-based cohort retrospective analysis	N = 35975 (colonoscopy cohort)	Up to 10 years	Incidence of colorectal cancer measured by SIR	SIR 0.69 (95% CI, 0.59-0.81) at 6 months, 0.66 (95% CI, 0.56-0.78) at 1 year, 0.59 (95% CI, 0.48-0.72) at 2 years, 0.55 (95% CI, 0.41-0.73) at 5 years, and 0.28 (95% CI, 0.09-0.65) at 10 years.	**III** Screening colonoscopies do not need to be performed at intervals shorter than 10 years.

Quality assessment: good representativeness and reliability of the exposures of the cohort as the population selection was obtained matching two registers (the Manitoba Cancer registry and the Manitoba health population registry)-avoidance of recall bias. Colorectal cancer incidence in thecohort was compared with the age-, sex-, and calendar-year−adjusted CRC incidence rates in Manitoba and expressed as standardized incidence ratios (SIRs). Adequate follow up.

Author, publication year	Intervention	Study design	Participants	Outcome	Results	Level of evidence Conclusions
Brenner 2006	Cases: patients with a first diagnosis of primary invasive colorectal cancer detected because of symptoms or incidentally (rather than by screening) were included Controls: community based control subjects	Population based case-control study	Cases = 380 Controls = 485 Germany 30 years old or older	To assess the long term risk of clinically manifest colorectal cancer among subjects with negative findings at colonoscopy	Negative colonoscopy Any time ago Cases: 30 (7.9%) Control: 134 (27.6%) Adj OR = 0.26 (95% CI 0.16-0.40) Negative colonoscopy 1–2 years ago Cases: 7 (1.8%) Control: 50 (10.3%) Adj OR = 0.16 (95% CI 0.07-0.36) Negative colonoscopy 3–4 years ago Cases: 8 (2.1%) Control: 31 (6.4%) Adj OR = 0.29 (95% CI 0.13-0.68) Negative colonoscopy 5–9 years ago Cases: 5 (1.3%) Control: 23 (4.7%) Adj OR = 0.25 (95% CI 0.09-0.69) Negative colonoscopy 10–19 years ago Cases: 5 (1.3%) Control: 17 (3.5%) Adj OR = 0.33 (95% CI 0.12-0.91) Negative colonoscopy 20+ years ago Cases: 5 (1.3%) Control: 13 (2.7%) Adj OR = 0.46 (95% CI 0.16-1.32)	IV Subjects with previous negative colonoscopy had a 74% lower risk of colorectal cancer than those without previous colonoscopy .This low risk was seen even if the colonoscopy had been done up to 20 or more years previously. Time interval could be extended to 20 years, or if repeat colonoscopies might not be needed at all

Quality assessment: community based control subjects matched with respect to age, sex, and county of residence; data collected through standardised personal interviews (trained interviewers); when possible, information on diagnostic process was confirmed by pertinent medical records comparability. Odds ratio were adjusted for age, sex, education, participation to general health screening examination, family history of CRC, smoking body mass index, ever regular use of NSAIDs and HRT.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Imperiale 2008	Retrospective study USA	1,256 participants 50 years of age or older, asymptomatic, without personal history of colorectal cancer, adenomatous polyps, or inflammatory bowel disease who had undergone first-time screening colonoscopy with no adenomatous polyps identified and underwent follow-up colonoscopy at 5 years	Polyp incidence Advanced adenoma incidence CRC incidence RR of any adenoma in people with hyperplastic polyps at baseline vs people with no hyperplastic polyps RR of advanced adenoma in people with hyperplastic polyps at baseline vs people with no hyperplastic polyps	5 years	Polyp incidence:16% Advanced adenoma incidence: 1.3% CRC incidence: 0 RR of any adenoma in people with hyperplastic polyps at baseline vs people with no hyperplastic polyps: 1.62 (CI95%1.21–2.15) RR of advanced adenoma in people with hyperplastic polyps at baseline vs people with no hyperplastic polyps: 1.77 (CI95%0.61–5.14)	**III** Among persons with no colorectal neoplasia on initial screening colonoscopy, the 5-year risk of colorectal cancer is extremely low. The risk of advanced adenoma is also low, although it is higher among men than among women. Our findings support a rescreening interval of 5 years or longer after a normal colonoscopic examination

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Lakoff 2008	Retrospective cohort study USA	110,402 patients aged 50 to 80 years who had a negative complete colonoscopy between January 1, 1992, and December 31, 1997, was identified by using linked administrative databases. We excluded those with a prior diagnosis of CRC, individuals with a prior diagnosis of inflammatory bowel disease and those who had undergone a colonic resection within 5 years before the index colonoscopy. We also excluded individuals who lived in the South East Local Health Integration Network, whose claims for services are not recorded in administrative databases. In the remaining Ontario population, 2,859,087 met the exclusion criteria and did not have a colonoscopy (controls).	RR of proximal, distal and any CRC in people with negative colonoscopy compared to people with no colonoscopy	7-14 years	RR of any CRC at 5 years follow up: 0.56 (CI95%0.46–0.67) RR of any CRC at 10 years follow up: 0.45(CI95% 0.34–0.55) RR of any CRC at 14 years follow up: 0.25 0.(CI95% 0.12–0.37)\n\nRR of proximal CRC at 5 years follow up: 0.72 (CI95%0.50–0.94) RR of proximal CRC at 10 years follow up: 0.57 (CI95%0.39–0.76) RR of proximal CRC at 14 years follow up: 0.23 (CI95%0.03–0.44) In the first five years follow up the reduction of CRC incidence was not statistically significant, and at 2 and 3 years follow up there was an increase of incidence, respectively statistically significant and non significant RR of distal CRC at 5 years follow up: 0.36 (CI95%0.25–0.47) RR of distal CRC at 10 years follow up: 0.34 (CI95%0.19–0.48) RR of diastal CRC at 14 years follow up: 0.21 (CI95%0.05–0.36)	III\n\nThis study has shown that a negative complete colonoscopy was associated with a subsequent reduced incidence of CRC overall, and of incident CRC in the distal colon over a 14 years follow up. However, the reduction in incidence of proximal CRC differed in magnitude and timing. The reduced incidence of proximal CRC was observed in about half of the 14 follow-up years, and mainly occurred after 7 years of follow-up

Quality assessment: Population truly representative of the population at average risk; Non exposed cohort drawn form the same community as the exposed cohort; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; No adjustment for confounding factors; Subjects lost to follow 28.6%; description provided of those lost.

Author, publication year	Study design Study objective	Participants	Outcomes	Follow up	Results	Level of evidence
Brenner 2007	Case control study Germany to assess the risk of CRC among patients with polypectomy (compared with subjects who never underwent large bowel endoscopy)	454 Patients with a first diagnosis of invasive CRC aged 30 or older 391 Community-based control subjects were randomly selected from population registries, employing frequency matching with respect to age, sex, and county of residence	CRC incidence CRC mortality among subjects who received colonoscopy with polypectomy compared to subjects who did not underwent colonoscopy	Up to 10 years	CRC incidence Polypectomy up to 10 year ago OR: 0.43 (0.25–0.74) Polypectomy up to 2 years ago 0.16 (0.06–0.43) Polypectomy up to 3-5 years ago 0.27 (0.08–0.87) Polypectomy up to 6-10 years ago 1.90 (0.67–5.43) People with advanced adenoma removed at baseline Polypectomy up to 10 year ago OR: 0.50 (0.23–1.12) Polypectomy up to 5 years ago 0.27 (0.10–0.77) Polypectomy up to 6-10 years ago 2.09 (0.41–10.69) People with no advanced adenoma removed at baseline Polypectomy up to 10 year ago OR: 0.36 (0.18–0.76) Polypectomy up to 5 years ago 0.14 (0.05–0.43) Polypectomy up to 6-10 years ago 1.76 (0.45–6.85)	IV Compared with subjects who had never undergone large bowel endoscopy, subjects with a history of polypectomy had a strongly and significantly reduced risk of colorectal cancer for up to 5 yr, even after detection and removal of high-risk adenomas. Although a nonsignificantly increased risk was found between 6 and 10 yr after polypectomy, overall risk reduction within 10 yr following polypectomy remained strong and statistically significant among patients for whom no high-risk adenomas were recorded.

Quality assessment: case definition by record linkage. Community controls subjects. Most important factor for adjustment done (age, sex, and county of residence. level of school education (categories: ≤9 yr, 10–11 yr, 12+ yr), history of CRC among a first-degree relative, smoking (categories: never, ever, current), ever regular use (at least once per month for at least 1 yr) of nonsteroidal anti-inflammatory drugs (NSAIDs), any hormone therapy (HT), and body mass index (categories <20, 20–24.9, 25–29.9, 30+ kg/m2). Ascertainment of exposure by interview not blinded to case /control status. Same rate of non response rate for both group.

Author, publication year	Study design Study objective	Participants	Outcomes	Follow up	Results	Level of evidence
Joergensen 2007	Retrospective study Denmark to demonstrate a possible benefit from long term (1_24 years) colonoscopic surveillance in a population of patients with all types of adenomas regardless of size and way of removal	2,041 patients included from year 1978 to 2002 were between 24 and 76 years old (average 60.8 years for men and 60.1 for women) at the initial adenoma removal. Intervals between planned colonoscopies varied between 6 and 48 months	CRC incidence CRC mortality The relative risk (RR) of CRC and death from CRC in the total study population was calculated from 1978 to 2002 by dividing the observed number by the number expected in a standard Danish population with the same age and sex distribution. The estimates of RR were adjusted for differences in the age, sex, and calendar specific rates.	Up to 24 years	CRC incidence RR: 0.65 (CI95% 0.43_0.95) CRC mortality RR 0.12 (CI95% 0.03_0.36) Overall mortality RR: 0.93 (CI95% 0.86_1.01)	**IV** In a population of patients with all types of adenomas, subjected to initial removal and following colonoscopic surveillance had a significant reduction of incidence (35%) of CRC as well as mortality (88%) from CRC compared to a standard population. Long-term colonoscopic surveillance may reduce incidence of CRC as well as mortality in patients with sporadic adenomas.

Quality assessment: Population truly representative of the population with adenomas. Ascertainment of exposure by clinical records. Assessment of outcome by record linkage.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Nusko 2008	Prospective cohort study Germany	1,091 patients with at least one follow-up examination documented after having an adenoma removed at initial total colonoscopy. 573 had metachronous adenomas during surveillances;	Relative risk (RR) for the development of metachronous adenomas of advanced pathology depending on the baseline findings. The time of surveillance until the detection of metachronous adenomas was determined as recurrence period. By the time the metachronous adenomas were removed and a clean colon was re-established, a second recurrence period started lasting until further metachronous lesions were found. Thus, four subsequent recurrence periods could be observed in our study group. We calculated incidence rates (IR) for two groups (for example: IR for a large adenoma in the next examination if patients had a small one in the present examination divided by the IR for a large adenoma in the next examination if patients had a large one in the present examination). The relative risk (RR) was calculated a s the quotient of the IR for the group with higher risk and the IR of the group with the lower risk.	Up to 25 years	Adenoma size: The metachronous adenomas of all generations of recurrence were significantly smaller than the initial lesions (p<0.0001). Histological type: In comparison with the initial lesion, the adenomas of the second (p=0.0003), third (p=0.002), and fourth generation (p=0.007) were significantly more often classified as tubular adenomas Degree of dysplasia: In the first recurrence, exclusively low-grade dysplasia was found significantly more often (p<0.00001). In comparison with the initial lesion, the second generation also showed a significantly (p<0.0001) less high-grade dysplasia. During surveillance, high-grade dysplasia was a rare event Advanced pathology: The first metachronous adenomas are significantly more often not advanced lesions (75.6%) compared with the initial findings (p<0.0001). In comparison with the initial lesion, the adenomas of the second (p<0.0001), third (p<0.0001), and fourth generation (p<0.0001) were also significantly more often classified as not advanced adenomas. Patients who had adenomas of advanced pathology at the initial examination have a significantly higher relative risk (RR 1.51; 95%CI 1.04–1.93) for advanced metachronous adenomas at the first recurrence. In the further generations of recurrence, the sample size was not sufficient to give evidence of an elevated relative risk. 2nd recurrence. RR 1.37 (CI95% 0.92–1.41) 3rd recurrence: RR 2.16 (CI95%0.55–5.21) 4th recurrence: RR 1.13 (CI95%0.11–11.57)	III Patients who had, at the baseline examination, large adenomas or tubulovillous or villous adenomas or multiple adenomas have a significant higher risk for those lesions also at follow-up. This finding may substantiate the necessity of a long-term risk-related surveillance of adenoma patients.

Quality assessment: Population truly representative of the population at average risk; Non exposed cohort drawn form the same community as the exposed cohort; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; No adjustment for confounding factors; Subjects lost to follow: data on surveillance follow up available only for the half of patients who had an adenoma removed.

Author, publication year	Study design	Participants	Outcomes	Follow up	Results	Level of evidence
Cafferty 2007	Retrospective cohort study Taiwan	2,287 patients who received baseline colonoscopy and at least one colonoscopy at follow up. Individuals with invasive carcinoma at their baseline examination were excluded	Risk of any positive findings at follow up Risk of multiple polyps at follow up Risk of large polyps at follow up Risk of villous adenoma or cancer at follow up According to baseline findings Data were analysed using multivariate logistic regression for each of the following outcomes: any positive findings at follow-up; multiple (≥3) polyps at follow-up; ≥1 large (≥10 mm) polyps at follow-up; or ≥1 villous adenomas or cancer at follow-up. The independent variables considered were number of polyps at baseline (0, 1, 2, or ≥3), the largest polyp at baseline (none, <5 mm, 5–10 mm, ≥10 mm, or unknown), the worst histologic finding at baseline (none, nonadenomatous polyp, tubular or tubulovillous adenoma, villous adenoma, or unknown), age at examination (<40, 40–49, 50–59, 60–69, or ≥70 years), sex, and time since baseline examination.	Up to 28 years. The median time between baseline and follow-up examination was 15 months	Negative findings at baseline: 1,130 (49 %) Positive findings at baseline: 1,157 (51 %) Risk of any positive findings at follow up depending on baseline results 1 polyp at baseline vs none : OR 3.59 (CI95% 2.81–4.60) 2 polyps at baseline vs none: OR 6.46 (CI95% 4.73–8.83) ≥3 polyps at baseline vs none: OR 13.72 (CI95% 9.88–19.06) Risk of multiple polyp (≥3) at follow up 1 polyp at baseline vs none: OR 2.94 (CI95%1.64–5.29) 2 polyps at baseline vs none: OR 6.91 (3.78–12.62) ≥3 polyps at baseline vs none: OR 20.97(12.14–36.22) Risk of large polyp (≥10 mm) at follow up: <5 mm polyp at baseline vs none : OR 1.31 (CI95% 0.37–4.58) 5–10 mm polyps at baseline vs none : OR 6.07 (CI95% 1.86–19.82) ≥10 mm polyps at baseline vs none : OR 9.98 (CI95%3.15–31.61) Non Adenomatous Polyp at baseline vs none: OR 1.31 (CI95% 0.37–4.58) Tubular adenoma or Tubulovillous at baseline vs none: OR: 0.66 (CI95% 0.23–1.94) Villous adenoma at baseline vs none OR: 0.50 (CI95% 0.10–2.47) Risk of villous adenoma or cancer at follow up Non Adenomatous Polyp at baseline vs none: OR 0.88 (CI95%0.11–7.23) Tubular adenoma or Tubulovillous at baseline vs none: OR: 0.39 (CI95%0.10–1.53) Villous adenoma at baseline vs none OR: 13.72 (CI95% 4.80–39.16)	III The number of baseline polyps was a significant risk factor for both positive results and multiple polyps, more severe baseline histology was a risk factor for large polyps and villous adenomas/cancer, and larger baseline polyps were a risk factor for large polyps at follow up.

Quality assessment: Population not described; Non exposed cohort drawn form the same community as the exposed cohort; Ascertainment of exposure by clinical records; Assessment of outcome by record linkage; Adjustment for confounding factors: yes; Subjects lost to follow: 2534 patients had a second colonoscopy from the 15,498 patients who had a colonoscopy in the 28 years period.

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Author, publication year	Study Objective Study design	Study Participants	Intervention	Follow up	Outcomes	Results	Conclusion Levels of evidence
Blumberg D., 2000	To determine the appropriate surveillance for patients with a history of adenomatous polyps whose last colonoscopic examination was normal. Retrospective cohort study New Orleans, Louisiana	204 patients who had received three colonoscopies between January 1990 and January 1996: an initial colonoscopy with adenomatous polyps (positive for adenomas) and 2 follow-up colonoscopies (interim and final) The risk of adenomas and cancers at final follow-up colonoscopy was compared between patients having a normal interim colonoscopy and those with a positive interim colonoscopy.	Surveillance colonoscopy in patients with a history of adenomatous polyps	2 follow colonoscopies: interim and final: median follow up 55 months	Risk of adenomas	Initial examination= 603 adenomas median follow-up, 55 months: 493 adenomas and 1 cancer **Interim follow-up (36 months)** Normal result: 91(45%) Positive (additional colonic neoplasm): 113 (55%) Incidence: Normal interim *vs* positive interim=15% *vs* 40% p=0.0001 **Final follow-up:** **Incidence of high-risk polyps (≥1cm or ≥3 polyps)** Normal interim *vs* positive Polyps at final colonoscopy: 34 vs 67 Polyp size <1: 17/34 (50) vs 32/67 (48) ≥1: 17/34 (50) vs 35/67 (52) RR=1.1 (95%CI=0.5-2.5) p=0.8 Polyp number 1-2: 27/34 (79) vs 43/67 (64) ≥3: 7/34 (21) vs 24/67 (52) RR=2.2 (95%CI=0.8-5.7) p=0.1 By 40 months, adenomas were detected in more than 40 percent of patients in both groups. The risk after a normal interim colonoscopy was not affected by time interval or number or size of polyps.	**III** In patients with a history of adenomas, a normal follow-up colonoscopy is associated with a statistically but not clinically significant reduction in the risk of subsequent colonic neoplasms. These patients require follow-up surveillance colonoscopy at a four-year to five-year interval.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record; adjustment for multiple prognostic factor; none lost at follow up.

Author, publication year	Study Objective Study Design	Participants	Outcome	Follow up	Results	Conclusion Level of evidence
Boparai 2010	to describe the clinical and pathological features of a large hyperplastic polyposis syndrome (HPS) cohort during multiple years of endoscopic surveillance. Retrospective cohort study	Clinical records of 77 patients with HPS from the period 1982e2008 were analysed retrospectively in this study	Incidence of CRC	Mean 5.6 years (range: 0.5e26.6)	In 35% patients CRC was detected of which 22 (28.5%) at initial endoscopy. CRCwas detected during surveillance in five patients (cumulative incidence: 6.5%) after a median follow-up time of 1.3 years and a median interval of 11 months. Of these interval CRCs, 4/5 were detected in diminutive serrated polyps (range: 4e16 mm). The cumulative risk of CRC under surveillance was 7% at 5 years. At multivariate logistic regression, an increasing number of hyperplastic polyps (OR 1.05, p¼0.013) and serrated adenomas (OR 1.09, p¼0.048) was significantlyassociated with CRC presence.	**III** HPS patients undergoing endoscopic surveillance have an increased CRC risk. The number ofserrated polyps is positively correlated with the presence of CRC in HPS, thus supporting a 'serrated pathway' to CRC. To prevent malignant progression, adequate detection and removal of all polyps seems advisable. If this is not feasible, surgical resection should be considered.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Ascertainment of exposure**:** secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	Participants	Outcome	Follow up	Results	Conclusion Level of evidence
Bressler 2004	to estimate the proportion of right sided colon cancers missed during colonoscopy. Case control study	4920 patients with a new diagnosis of right sided colorectal cancer, Patients who had a colonoscopy within 3 years of their diagnosis were divided into 2 groups: detected cancers (those who had a colonoscopy up to 6 months before the diagnosis) and missed cancers (those who had a colonoscopy between 6 and 36 months before the diagnosis)	Missed cancer during colonoscopy		53.9% had at least 1colonoscopy within 3 years of their index admission. Of these 2654 who had a colonoscopy, 88.9% had a complete procedure (i.e., the cecum was visualized), and most (96.0%) had their most recent colonoscopy up to 6 months before admission Of these 2549 patients (the detected-cancer group), 89.0% had a complete colonoscopy. Of the 2654 patients who had a colonoscopy, 105 patients (4.0%) had their most recent colonoscopy between6 and 36 months before their index admission : missed cancer. Of these 105 patients (the missed-cancergroup), 86.7% had a complete procedure	**IV** Among persons undergoing resection for right-sided colon cancer, the miss rate of colonoscopy for detecting cancer in usual clinical practice was 4.0%.

Quality assessment: adequate case definition by record linkage; consecutive series of cases; hospital controls; no adjustment for confounding factors; ascertainment of exposure by record linkage; Same method of ascertainment for cases and controls.

Author, publication year	Study Objective Study Design	intervention	Participants	Outcomes	Results	Conclusion Level of evidence
Costantini M., 2003	To evaluate the interobserver agreement of four pathologists in the histologic classification of polyps (hyperplastic vs. adenomas), and, in the subgroup of polyps classified as adenomas, the histologic type and the degree of dysplasia or the presence of infiltrating carcinoma. Study aimed to assess interobserver agreement Italy	4 Pathologists reviewed diagnosis of 100 colorectal polyps	Stratified random sample of 100 polyps from the 4,889 polyps resected within the Multicentre Adenoma Colorectal Study (SMAC) in 2579 subjects. The slides were blindly reviewed by the four pathologists, one from each center participanting. Reference standard: WHO classification	Interobserver agreement	Perfect **agreement** in the diagnosis of histology among the four pathologist for 48/100 polyps **% polyps classificated as hyperplastic (vs adenoma) by pathologists** A=19% B=14% C=20% D=19% **Interobserver agreement for the diagnosis of hyperplastic polyp vs adenoma, kappa (95% CI)** Median: 0.89 (0.79-1.00) Overall: 0.90 (0.82-0.98) *Classification of adenomas according to the histologic type was significantly different among the four pathologists* **Interobserver agreement by histologic type, kappa median** Tubular= 0.50 (0.36-0.87) Tubulovillous= 0.15 (-0.09-0.21) Villous= 0.36 (0.16-0.51) Overall kappa (tubular vs tubulovillous)=0.34 (0.28-0.41) **Interobserver agreement by degree of dysplasia, kappa median** Low grade= 0.53 (0.47-0.69) High grade= 0.39 (0.25-0.57) Infiltrating carcinoma= 0.78 (0.73-0.84) Overall kappa =0.54 (0.48-0.61) **Interobserver agreement by degree of risk, kappa median** Low risk= 0.52 (0.46-0.66) High risk= 0.45 (0.30-0.60) Elegible for surgery= 0.23 (-0.04-0.56) Overall kappa =0.47 (0.39-0.55) 12 polyps classified as infiltranting carcinoma	**V** Data show that agreement among pathologists in current clinical practice is acceptable only for differentiation between hyperplastic and adenomatous polyps. Among polyps classified as adenomas, the observed agreement in the identification of adenoma histologic types and degree of dysplasia was unsatisfactory. Most important, concordance level was not acceptable at all for the diagnosis of infiltrating carcinoma.

Author, publication year	Study Objective Study Design	Participants	Outcome	Follow up	Results	Conclusion Level of evidence
Farrar 2006	To determine whether interval colorectal cancers were associated with an inadequate earlier colonoscopy, incomplete polypectomy, or aggressive biologic behavior. Retrospective cohort study	830 patients diagnosed with colorectal cancer during the study period	Interval cancer Patients were defined as having an interval cancer if they developed colorectal cancer within 5 years of a complete colonoscopy	5 years	**Interval cancer** 5.4% (95% confidence interval [CI], 4.1%–7.2%) of all colorectal cancers diagnosed The index colonoscopy was normal in 33%; of patients who went on to develop interval cancers.. In 27%o f patients an interval cancer developed at the same segment of the colon from which a polyp had previously been removed. There was no association between interval cancers and any individual endoscopist, endoscopist level of experience, or the involvement of a trainee endoscopist during colonoscopy. There were no differences in interval cancers and sporadic cancers with regard to quality of bowel preparation, patient age or gender, presence of polyps, or other colonoscopic findings like diverticulosis Colorectal cancer occurred in the right colon in 51% of patients with interval cancer, compared with 29% with sporadic cancer ($P\_$ .011) Interval cancers were smaller in size than sporadic cancers (3.5 vs 4.4 cm; P :.017). No patient characteristics, factors that influence the quality of colonoscopy, or markers of aggressive tumour behaviour were found to be independently predictive of interval cancers. However, interval cancers differed from sporadic cancers in regard to tumour location and size. After adjusting for age and tumour stage, interval cancers were more likely to be located in the right colon OR: 2.9; 95% CI, 1.2–6.4 and were smaller in size (OR, 1.3; 95% CI, 1.0 –1.6) than sporadic cancers	**III** Interval colorectal cancers differed from sporadic colorectal cancers with regard to location and size but not markers of aggressive biologic behavior. Although we were unable to identify any factors that influence the quality of colonoscopy that were predictive of interval cancer, we found that 27% of interval cancers occurred in the same segment of the colon from which a polyp had been removed at previous colonoscopy. This suggests that incomplete polyp resection might have played an important role and warrants further investigation.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Heresbach D., 2008	To assess the adenoma miss rate while limiting technique or operator expertise biases, with same-day back-to-back video colonoscopy, done by two different operators in randomised order and blinded to the other examination. Prospective multicenter study France	294 patients from 11 centers undergoing the same day back-to-back video colonoscopy, done by two different operator in randomised order (by using thae last name of operator) and blinded to the result of the first examination. N=286 (only these were available for comparison): 147 men; median age 54.4 years (range 20-88)	Back- to-back video colonoscopies, done by two different operators	Miss rate for colorectal neoplastic polyps	**Miss rate (lesion missed at first examination/seen at first or second examination)** Polyps= 28% (155/556) Hyperplastic polyp=31(55/175) Polyp≥5 mm=12 (14/119) Adenoma=20 (37/175) Adenoma<5 mm=27 (29/110) Adenoma≥5 mm=9 (6/65) Advanced adenoma=11 (3/27) Carcinoma=0 (0/4) Multiple logistic regression analysis of the 155 missed polyps among the total 556 polyps: histological type was not associated with the decrease in the miss rate for polyps; diameter (1 mm increments) and number of polyps (≥3) were independently associated with a decrease in the miss rate for polyps. **Per patient specific miss rate for lesion type, % (95%CI)** Any Polyps= 36 (29-43) Adenomas=26 (18-36) Polyp≥5 mm=17(10-26) Adenoma≥5 mm=11 (4-22) Advanced adenoma=11 (2-30) Carcinoma=0 **Per patient overall 8among 286 patients) miss rate for lesion type, % (95%CI)** Any Polyps= 23.4 (18.6-27.8) Adenomas=9.4 (6.3-13.4) Polyp≥5 mm=5.2(2.9-8.5) Adenoma≥5 mm=2.1 (0.8-4.5) Advanced adenoma=1 (0.2-3.0) Carcinoma=0	**III** The study confirms a significant miss rate for polyps or adenoma during colonoscopy. The miss rates for polyps, adenomas, polyps ≥ 5 mm, adenomas ≥ 5 mm, and advanced adenomas were, respectively, 28%, 20%, 12%, 9% and 11%.. The specific lesion miss rates for patients with polyps and adenomas were respectively 36% and 26% but the corresponding rates were 23% and 9.4% when calculated for all 286 patients.

Quality assessment: allocation concealment: adequate; blindness of provider: yes; blindness of outcome assessor: no; 8 patients didn't complete the study.

Author, publication year	Study Objective Study Design	Participants	Outcome	Follow up	Results	Conclusion Level of evidence
Hyman 2004	To define the cancer risk associated with hyperplastic polyposis. Prospective case series	Thirteen patients who met the criteria for hyperplastic polyposis. Presence of >20 hyperplastic polyps and/or a hyperplastic polyp _ 1 cm in size in the right colon. The HPs had to be distributed throughout the colon, rather than just concentrated in the rectosigmoid..	Incidence of CRC	Not reported	All of these patients had at least 30 polyps distributed throughout the colon, often >100. Nine of 13 also had a hyperplastic polyp at least 1 cm in size, usually in the right colon 54 percent developed colorectal cancer during the study period. Four had a cancer on initial diagnosis of hyperplastic polyposis, and an additional three patients developed colorectal cancer despite at least every other year colonoscopic surveillance.	V Patients with hyperplastic polyposis are at high risk for colorectal cancer

Author, publication year	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Li 2009	To determine the association between the presence of large serrated colorectal polyps and synchronous advanced colorectal neoplasia. Cross-sectional study	467 cases of advanced colorectal neoplasia (tubular adenoma ≥ 1 cm, adenoma with any villous histology, adenoma with carcinoma *in situ* / high-grade dysplasia, or invasive adenocarcinoma) 4247 controls without advanced neoplasia All selected Among 4,714 asymptomatic subjects who underwent screening colonoscopy	Predictors of advanced neoplasia assessed by multivariate logistic regression(age, sex, family history of colorectal cancer, body mass index, the presence and number of small tubular adenomas (<1 cm), the presence of multiple small serrated polyps (<1 cm), and the presence of large serrated polyps (≥ 1 cm)	Independent predictors of advanced colorectal neoplasia were increasing age (odds ratio (OR) = 4.51; 95 % confi dence interval (CI), 1.43 – 14.3; P = 0.01 for subjects ≥ 80 years vs. 50 – 54 years of age); non-advanced tubular adenomas (OR = 2.33; 95 % CI 1.37 – 3.96, P = 0.0017 for 3 or more); and large serrated polyps (OR = 3.24; 95 % CI 2.05 – 5.13, P <0.0001). In total, 109 subjects (2.3 % of the study population) had large serrated polyps. Right- and left-sided large serrated polyps had a similar association with advanced colorectal neoplasia (OR = 3.38 vs. 2.66, P = 0.62).	V Large serrated polyps are strongly and independently associated with synchronous advanced colorectal neoplasia. Our results suggest that large serrated polyps may be a marker for advanced colorectal neoplasia. Further studies are needed to determine whether the association with advanced neoplasia differs among subsets of serrated polyps, particularly SSAs and classic hyperplastic polyps.

Author, publication year	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Lieberman 2008	To determine rates of advanced histology in patients undergoing colorectal cancer screening whose largest polyp is 9 mm or less.. Cross-sectional study	6,360 asymptomatic patients with polyps, with complete histology available in 5977 (94%). among 13,992 asymptomatic patients who had screening colonoscopy	Proportion of patients with advanced histology among patients with polyps found at screening colonoscopy	Among 3,744 patients whose largest **polyp was 1–5 mm**, the polyp histology was neoplastic in 50.2% and advanced in 1.7%. Among 1,198 patients whose largest **polyp was 6–9 mm**, histology of most advanced polyp was neoplastic in 67.7% and advanced in 6.6%, and 0.92% had either cancer or adenoma with high-grade dysplasia Among 949 patients whose largest **polyp was ≥10 mm**, polyp histology was neoplastic in 82.0%, with advanced histology in 30.6%. There was a progressive increase in the proportion of polyps with advanced histology with increasing size above 10 mm The proportion of polyps with advanced histology was 18.9% in 10- to 14-mm polyps, 31.7% in polyps 15–19 mm, 42.3% in polyps 20–24 mm, and 75% in polyps _25 mmhistology of most advanced polyp was neoplastic in 67.7% and advanced in 6.6%, and 0.92% had either cancer or adenoma with high-grade dysplasia	**V** One in 15 asymptomatic patients whose largest polyp is 6 to 9 mm will have advanced histology.

Author, publication year	Study Objective Study Design	Inclusion criteria	Intervention compared	Outcome	Results	Conclusion Level of evidence
Martinez 2009	To asses the risk of developing advanced adenomas and cancer after polypectomy or the factors that determine risk Systematic review	Inclusion criteria : 800 or more study participants; (2) study protocol requiring complete baseline colonoscopy with removal of one or more adenomas and removal of all visualized lesions; (3) a specified schedule of surveillance follow-up colonoscopies; and (4) available end point data regarding the number, size, and histopathology of adenomas and colorectal cancers detected in follow-up examinations	Relation between patient characteristics or features of the baseline adenoma with risk of metachronous neoplasms	Advanced neoplasia diagnosed during an interval beginning 6 months after the baseline examination and ending on the date of the last protocol-specified colonoscopic examination Risk factor for developing advanced neoplasia : sociodemographic variables (age, sex, and race), BMI, cigarette smoking, family history of colorectal cancer in first-degree relatives, and history of polyps or adenomas before the baseline examination. baseline adenoma characteristics (number, size, location, histology, and high-grade dysplasia)	8 studies included, 6 RCTs , 9167 patients Risk of a metachronous advanced adenoma was higher among patients with 5 or more baseline adenomas (24.1%; standard error, 2.2) and those with an adenoma 20 mm in size or greater (19.3%; standard error, 1.5). Risk factor patterns were similar for advanced adenomas and invasive cancer. In multivariate analyses, older age ($P <.0001$ for trend) and male sex (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.19 – 1.65) were associated significantly with an increased risk for metachronous advanced neoplasia, as were the number and size of prior adenomas ($P <.0001$ for trend), the presence of villous features (OR, 1.28; 95% CI, 1.07–1.52), and proximal location (OR, 1.68; 95% CI, 1.43–1.98). High-grade dysplasia was not associated independently with metachronous advanced neoplasia after adjustment for other adenoma characteristics	III Occurrence of advanced colorectal neoplasia is common after polypectomy. Factors that are associated most strongly with risk of advanced neoplasia are patient age and the number and size of prior adenomas.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	NOT REPORTED
	Date restriction	up to June 2005.
	any restriction	only English published studies done in North America
Selection	Inclusion and exclusion criteria	complete baseline colonoscopy with removal of one or more adenomas and removal of all visualized lesions; (3) a specified schedule of surveillance follow-up colonoscopies; and (4) available end point data regarding the number, size, and histopathology of adenomas and colorectal
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	adjusted odds ratios (ORs) for the study end points using logistic regression models that controlled for study, age, sex, race, smoking status, BMI, family history of colorectal cancer, history of polyp or adenoma before the baseline examination, and the baseline adenoma characteristics
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	yes

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Neklason 2008	To asses adenoma risk based on the degree of relationship to CRC cases in the first-, second-, and third-degree relatives of CRC cases cross-sectional study	Families were identified from the Utah Population Database as having a statistical excess of colorectal cancer as compared to the database as a whole. Two-hundred sixty-two relatives of 36 CRC cases were invited to participate, and 236 of these (90%) underwent colonoscopy of which 185 were prospective and 51 retrospectively analysed Families with Lynch syndrome and hereditary polyposis were excluded	Colonoscopy performed in the relatives of CRC cancer In order to study the effect of degree of relation on the incidence of colon neoplasms, the kindred members were separated into three groups. The first-degree relative group consists of individuals with at least one first-degree relative (parents, sibling, or child) diagnosed with colorectal cancer. The second-degree relative group is composed of individuals with no affected first-degree relative but at least one second-degree relative (aunts, uncles, grandparents, or grandchildren) diagnosed with colorectal cancer. The third-degree relative group is composed of individuals with no affected first- or second- degree relative but a third-degree relative affected with colorectal cancer.	Prevalence of adenomatous polyp formation Risk factor for adenomatous polyp formation:	Advanced adenomatous polyps were found in 20 individuals, that is 37% of relatives were found to have adenomas on colonoscopy. The average age of diagnosis for colon cancer was 63 years and advanced adenomas 56 years. Independent predictors of adenomatous polyps in the relatives were advancing age (p<0.0001), male gender (p<0.001), and greater degree of relation to colorectal cancer cases (p<0.01). There was no significantpredilection of colorectal tumours for the right or left colon. A higher degree of relationship to CRCcases was a significant predictor of having simple and advanced adenomas, but not hyperplastic polyps after adjustment for age and gender.	V These data support the current recommendations for colonoscopy starting before the age of 50 years in individuals with a strong family history of colorectal cancer

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Noshirwani 2000	To identify whether patient or adenoma characteristics at an initial colonoscopy could help predict populations at high and low risk of significant polyp formation within 3 years. In addition, we wanted to calculate the risk associated with each additional adenoma found at the baseline examination retrospective cohort study	697 patients identified from the Cleveland Clinic Foundation Adenoma Registry records data seen between 1979 and 1989 who had 1 or more adenomas removed at colonoscopy and a surveillance examination within 10 to 42 months (mean 18 months). Patients with colon cancer, ulcerative colitis and familial adenomatous polyposis were excluded	Surveillance examination within 10 to 42 months (mean 18 months	Incidence of adenoma at first follow up Risk factor for adenoma recurrence after polypectomy	**OR of recurrence** (multivariate analysis) Age (per 10-year increase) OR: 95%CI 1.10 0.82, 1.45 Gender (male vs. female) OR 1.48 95%CI 0.74, 2.93 Number (per 1 increase) 1.25 95%CI 1.13, 1.38 Size of adenoma removed (≥ 1 cm vs. <1 cm)OR: 3.68 95%CI 2.01, 6.76 Pathology (tubular adenoma vs. others) OR 1.37 95%CI 0.72, 2.62 Interval between examinations (per 6-month increase) OR 0.85 95%CI 0.66, 1.09 Having 3 or more adenomas on initial colonoscopy with at least 1 measuring 1 cm or larger greatly increased the chance of a significant finding on the first surveillance colonoscopy. Conversely, patients with 1 or 2 adenomas all measuring less than 1 cm were at extremely low risk of an important outcome within 3 years.	**III** Patients with 1 or 2 adenomas all measuring less than 1 cm are an identified low risk group and their first surveillance examination may be delayed beyond the standard 3 years.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Non exposed cohort drawn from the same community; Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	Characteristic of participants	Intervention	Outcome	Results	Conclusion Level of evidence
Nusko 2002	To identify whether Adenoma size, histological type, site, andmultiplicity, together with patient age and sex, are risk factors for the presence of high grade dysplasia or invasive carcinoma in adenomas retrospective cohort study	Follow up records of 1159 patients undergoing surveillance after polypectomy examinations were used as a basis to identify factors that might determine the risk of metachronous adenomas developing during follow up.	Surveillance examination; length of follow up not reported	Incidence of adenoma at follow up Risk factor for adenoma recurrence after polypectomy metachronous adenomas were defined as those detected more than 180 days after the initial clearing procedure	RR of recurrence (multivariate analysis) Size (>10 mm) RR 1.81 95%CI 1.42–2.31 Multiplicity RR 1.54 95%CI 1.12–2.12 Parental history RR 2.32 95%CI 1.77–3.04 Size (<10 mm), male RR 1 Size (<10 mm), female RR 0.95 95%CI 0.87–1.14 Size (>10 mm), male RR 1.81 95%CI 1.42–2.31 Size (>10 mm), female RR 1.08 95%CI 0.81–1.18 On the basis of multivariate analysis, two risk groups were identified: (1) patients with no parental history of colorectal carcinoma with only small (<10 mm) tubular adenomas at the initial clearing examination have a very low risk, and we estimated that 10% will develop advanced metachronous adenomas after 10 years; (2) the high risk group contained all other patients, 10% of whom will show metachronous adenomas ofadvanced pathology at follow up after only three years.	III The risk of developing metachronous adenomas with advanced pathology can be stratified for various patient and adenoma characteristics. Surveillance intervals can be scheduled for low risk (10 years) and high risk (three years) patients. Risk related follow up thus helps to avoid unnecessary examinations.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Non exposed cohort drawn from the same community; Ascertainment of exposure: secure record (eg clinical records); adjustment for multiple prognostic factor confounding by multivariate analysis. Assessment of outcomes by record linkage.

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Pabby 2005	To review the circumstances surrounding cancer occurrence in the Dietary Polyp Prevention Trial PPT and to identify factors associated with CRC detection case series	13 cancer case among 2,079 patients included in the trial who had one or more histopathologically confirmed colorectal adenomas removed during a qualifying colonoscopy within 6 months before randomisation	An algorithm was developed to classify each cancer into one of 4 etiologies: (1) incomplete removal (cancer at the site of previous adenoma), (2) failed biopsy detection (cancer in an area of suspected neoplasia with negative biopsy specimens), (3) missed cancer (large, advanced stage cancer found at a short interval after colonoscopy), or (4) new cancer (small, early stage cancer after a longer time interval)	4 incomplete removal, 3 failed biopsy detection, 3 missed cancers, and 3 new cancer cases.adenomas ofadvanced pathology at follow up after only three years. Of the patients with a diagnosis of cancer, 53.8% had a potentially ''avoidable'' reason for failed or delayed detection (missed lesion [3/13] or incomplete removal [4/13]) and 46.2% were determined to have an unavoidable reason for failed cancer detection (failed biopsydetection [3/13] or new cancer [3/13]).	**V** The risk of Interval cancer occurs despite colonoscopy. Improved quality of colonoscopy may have reduced cancer prevalence or resulted in earlier cancer detection in over 50% of prevalent cancers in the dietary Polyp Prevention Trial.

Author, publication year	Study Objective Study Design	Characteristic of participants	Follow up	Outcome	Results	Conclusion Level of evidence
Robertson 2005	To describe the risk of colorectal cancer occurring in the course of colonoscopic surveillance, we determined the frequency of invasive cancer and adenomas with high-grade dysplasia among patients followed up in 3 randomised trials of colorectal adenoma chemoprevention.retrospective cohort study	2,915 Patients drawn from 3 adenoma chemoprevention trials. All underwent baseline colonoscopy with removal of at least one adenoma and were deemed free of remaining lesions	Follow-up colonoscopies for patients in the first 2 trials were scheduled about 1 and 4 years after the clearing examination. Patients enrolled in the third trial were scheduled for surveillance olonoscopy about 3 years after the clearing examination.	Incidence of invasive cancer Risk factor for recurrence	**Overall Cancer Incidence**: 1.74 (95% CI, 1.05–2.72) per 1000 person years of follow-up. **Incidence in the first year of follow up**: 3.79 (95% CI, 1.63–7.47) per 1000 person-year **Incidence in the following 2-4 years**: 0.96 (95% CI, 0.31–2.24) per 1000 person-years The 26 patients diagnosed with an advanced neoplasm (cancer or adenoma with high-grade dysplasia) were older than those without such findings (mean age, 65.5 vs 59.6 years; P <.001) and had a greater mean number of prior lifetime adenomas (4.3 vs 2.5; P <.02). Patients who had a large (>1.0 cm) adenoma at the time they qualified for the trials seemed more likely to be diagnosed with an advanced neoplasm than were those who had smaller adenomas (1.24% vs 0.74%; P <.20), and men seemed more likely than women to have an advanced neoplasm (1.06% vs 0.5%; P <.08), although neither finding was statistically significant. Race, cigarette smoking history, and family history of colorectal cancer or adenoma were not related to risk of an advanced neoplasm	**III** Colorectal cancer occurs more frequently after complete colonoscopy than may be generally appreciated. Although these tend to be early lesions, informed consentfor this procedure should probably mention this risk, as recently recommended by a multidisciplinary task force.[34] Patients with a history of adenoma are a high-risk population for the development of colorectal cancer; although clinical trials[27] have addressed some key issues regarding the appropriate schedule of colonoscopic surveillance in these patients, much important work remains. For example, a better understanding of the factors that determine risk for subsequent cancer development will be important for tailoring surveillance recommendations to individual patients following adenoma removal. Future studies, either pooling data from large cohorts or perhaps a trial, are essential..

Author, publication year	Study Objective Study design	Study Participants	Intervention	Follow up	Outcomes	Results	Conclusion Levels of evidence
Schreiner M.A., 2010	To investigate whether detection of proximal nondysplastic serrated polyps (NDSP) at screening and surveillance colonoscopies is associated with advanced neoplasia. cohort study Oregon	3,121 asymptomatic patients (aged 50–75 years) who had screening colonoscopies at 13 Veterans Affairs medical centers between February 1994 an January 1997 1371 had subsequent surveillance.	Screening colonoscopy	Follow-up data included all procedures that occurred within 5.5 years post baseline on all subjects.	Rates of detection of any neoplasia and advanced neoplasia at screening and surveillance colonoscopies (within 5.5 years) in patients with and without proximal or large ND-SP	**Prevalence of advanced adenoma, % OR** *proximal ND-SP vs no proximal ND-SP:* 17.3% vs 10.0%, OR=1.90 (1.33-2.70) large *ND-SP vs* no large *ND-S:* 27.3% vs 10.3%, OR=3.37 (1.71-6.65) **Prevalence of ≥ 3 tubular adenomas, % OR** *proximal ND-SP vs no proximal ND-SP:* 10.7% vs 5.3%, OR=2.19 (1.36-3.52) large *ND-SP vs* no large *ND-S:* 9.4% vs 5.6%, OR=1.72 (0.52-5.73) **Follow up:** **At baseline no neoplasia** Advanced neplasia on follow-up CSP, n(%) With proximal ND-SP=2 (5.1) OR =2.09 (0.44-9.87) Without proximal ND-SP=11 (2.7) Any neoplasia on follow up, n(%) With proximal ND-SP=17 (43.6) OR =3.14 (1.59-6.20) Without proximal ND-SP=83 (20.0) **At baseline Small tubular adenoma <10mm** Advanced neplasia on follow-up CSP, n(%) With proximal ND-SP=5 (7.9) OR =1.23 (0.46-3.28) Without proximal ND-SP=36 (6.3) Any neoplasia on follow up, n(%) With proximal ND-SP=26 (41.3) OR =0.96 (0.57-1.63) Without proximal ND-SP=240 (41.8) **At baseline Advanced neoplasia** Advanced neplasia on follow-up CSP, n(%) With proximal ND-SP=11 (28.9) OR =2.25 (1.02-4.96) Without proximal ND-SP=36 (14.7)	**III** Detection of proximal and large ND-SP at a screening colonoscopy is associated with an increased risk for synchronous advanced neoplasia. Detection of proximal ND-SP in a baseline colonoscopy is associated with an increased risk for interval neoplasia during surveillance.

| | | | | | | Any neoplasia on follow up, n(%)
With proximal ND-SP=27 (71.1)
OR =2.17 (1.03-4.59)
Without proximal ND-SP=127 (51.8) | |

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record; adjustment for multiple prognostic factor; none lost at follow up.

Author, publication year	Study Objective Study Design	Characteristic of participants	Outcome	Results	Conclusion Level of evidence
Wark 2009	To evaluate whether a family history of colorectal cancer is associated with adenoma multiplicity or advanced adenoma stage. Cross-sectional survey	28,840 participants who responded to a questionnaire concerning family history of CRC and information on age, race, height, weight, physical activity, use of aspirin, smoking history and habits, alcohol consumption and whether the men underwent either colonoscopy or sigmoidoscopy in the past 2	Multinomial logistic regression was also used to compare the distributions of a family history of colorectal cancer among patients with multiple and single distally located adenomas, and men who did not report any adenomas. Multinomial logistic regression was also used to compare the distributions of a family history of colorectal cancer among patients with multiple and single distally located adenomas, and men who did not report any adenomas	1,496 men were classified as having advanced and 1,507 as having non advanced adenomas. 622 men had multiple and 1,985 had single adenomas in the distal colon and rectum. A family history of colorectal cancer was similarly associated with advanced and non advanced adenomas **advanced vs. nonadvanced**, OR 0.98 (95% CI 0.82–1.17), **advanced vs adenoma-free**: OR 1.67 (95% CI 1.47–1.91), **nonadvanced vs. adenoma-free** :OR 1.70 (95% CI 1.49–1.94)],. A family history of colorectal cancer was more strongly associated with multiple distally located adenomas **multiple vs. single**, OR 1.35 (95% CI 1.09–1.68), **multiple vs. no distally locate**d adenomas: 2.02 (95% CI 1.67–2.44), **single vs. no distally located** adenomas: 1.49 (95% CI 1.32–1.68). The number of adenomas was also positively associated with a family history of colorectal cancer. (1.06% vs 0.5%; *P*: .08	**V** At the population level, heritable factors may be more important in earlier stages of adenoma formation than at stages of adenoma advancement for at least distally located adenomas.

10
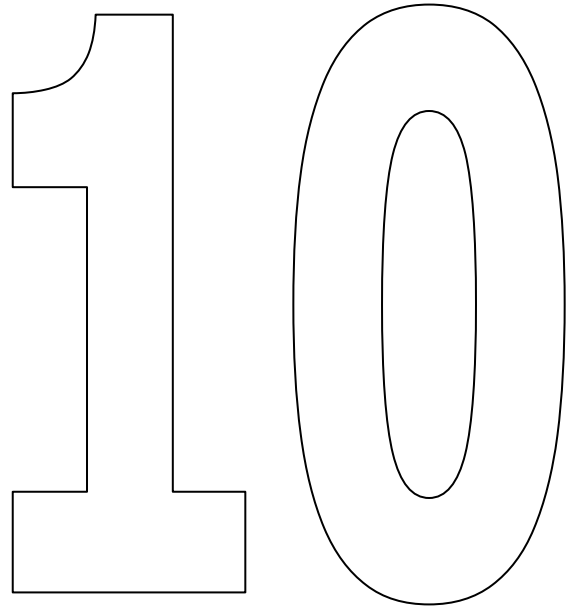
Communication
EVIDENCE

EU CRC Guidelines Literature Group

10.1 Evaluation of differences in the currently available strategies used for communicating information about colorectal cancer screening to health professionals and general public

10.1.1 Summary document

Rita Banzi and Silvia Minozzi

CLINICAL QUESTION 1

What are the currently available strategies used for communicating information about colorectal cancer screening to the general public?

PICOS

P: General population (asymptomatic individuals)
I: Population/patient information materials (print/written, verbal, computerised, DVD/video, slide-tape)
C: Not applicable
O: Decision-making, psycho-social outcomes (anxiety, worry, etc), knowledge, informed consent, informed choice, risk perception, attitudes/beliefs
S: Systematic reviews, RCT, CT, Cohort, Cross-sectional
AND

CLINICAL QUESTION 2

What are the currently available strategies used for educating or supporting health professionals for providing information about CRC screening to the general public?

PICOS

P: Health professionals
I: Information materials (print/written, verbal, computerised, DVD/video, slide-tape); further education courses/sessions, office support systems
C: Not applicable
O: Decision-making, discussions with patients
S: Systematic reviews, RCT, CT, Cohort, Cross-sectional
AND

CLINICAL QUESTION 3

What quality indicators are currently used to evaluate the effectiveness of communicating information to the general public concerning CRC screening?

PICOS

P: General population (asymptomatic individuals); Health professionals
I: Quality checklists, patient evaluation of materials, health professional evaluation of materials
C: Not applicable
O: Improved understanding, risk perceptions, knowledge
S: Systematic reviews, RCT, CT, Cohort, Cross-sectional

SEARCH METHOD

We searched MedLine, Embase and PsychInfo databases from 1988 (search strategies reported in Table 4). We also searched the Cochrane Library and retrieved additional papers from the analysis of the quoted bibliography.

RESULTS

Question 1

We found 54 reports relevant for this issue. We were unable to retrieve systematic reviews but, after the analysis of the full text publication, 25 RCTs were considered eligible (1-25).
We excluded 6 retrieved studies as they were cross-sectional or quasi experimental studies with a small sample size and likely not to add relevant information on this topic (26-31).

We also retrieved studies which report screening information programmes conducted in the USA on special populations, such as African American, Latinos, medical unserved and low income people, Hawaiian native. Considering the large socio-cultural differences between this population and the target of these European guidelines we decided not to include these studies. However, data are available if requested.

The included studies largely differ in terms of type of intervention, comparison, participants, setting, and evaluated outcomes. In order to try to summarise data we categorised studies on the basis of the type of intervention. We identified three categories:

- tailored intervention (adaptation of the intervention and/or total redesign to best fit the needs and characteristics of a target audience: telephone call, interactive decision aid, counselling, etc.);
- non tailored intervention (standard communication strategies: leaflet, printed material, mails, etc.);
- usual care (no intervention, usual referral or screening invitation).

We grouped studies on the basis of the type of comparison, specifically considering tailored vs. non tailored intervention, different intensity of non tailored intervention, tailored and non tailored vs. usual care.

Finally, we merged outcomes in three broad categories: 1) knowledge (both of screening opportunities and characteristics, and risk perception), 2) attitude and beliefs (including evaluation of barriers), and 3) behaviour (compliance with screening programme, decision-making).

We found seven RCTs addressing the comparison between tailored and non tailored intervention (1, 10, 13-15, 20, 21). Results are summarised in Table 1. Knowledge and attitude outcomes were evaluated in 2 studies (10, 14) but no significant differences were found: only a slight increase in readiness to attend screening and perception of screening self-efficacy was reported when a personally tailored interactive multimedia computer programme was compared with a non-tailored

electronic leaflet (10). Six out of seven studies investigated the effect of tailored programmes on screening participation rate. Tailored telephone calls and educational sessions performed by trained nurses increased FOBT compliance or participation to any CRC screening programme when compared to non tailored intervention (1, 21, 15).

We found eight RCTs addressing the comparison between different intensity of non tailored programmes (2, 6-8, 11, 12, 22, 24). Results are summarised in Table 2. Six out of 8 studies assessed knowledge (2, 6, 7, 8, 12, 11) and 4 out of 8 assessed attitude to screening (6, 8, 12, 24). Statistically significant results were found in 3 studies: a communication programme involving the "no screening" option increased the clarity of information and the overall rating on the screening perception.(7) Including illustrations or a detailed analysis of the decision options using the analytic hierarchy process within standard materials increased message clarity and knowledge of screening programmes.(2, 6) Different interventions aimed at explaining CRC risk in different modalities (absolute and relative risk) did not improve knowledge (11, 12). Interest and intent in undergoing screening were not improved by more intense communication programmes.

Only one out of three studies (6, 11, 22) assessing behaviour outcomes reported an improved compliance to CRC screening when an enhanced health promotion programme was added to a standard company-sponsored screening programme (22).

We found ten RCTs addressing the comparison between tailored (4, 16) and non tailored (3, 5, 9, 17-19, 23, 25) programme with usual care (no intervention, usual referral or screening invitation). Results are summarised in Table 3. Four out of ten studies reported knowledge and attitude outcomes. (17-19, 23) Information programmes regarding CRC risk factors increased knowledge and self efficacy perception of screening with no increase of negative attitudes (18, 19, 23). An education video produced only a slight increase of the number of ordered screening tests. (17) Eight out of ten studies assessed behaviour outcomes, two involving tailored interventions (4, 16) and six non tailored interventions (3, 5, 9, 17, 23, 25). Only one study reported and increase of percentage of screening tests following a tailored informational intervention. (16) Among non tailored interventions, mailed brochures and educational videos appeared to be effective in increase the screening participation rate when compared to standard screening invitation (3, 5, 17, 23).

Question 2

We were able to retrieve only one RCT which reports data on educational programmes dedicated to health professionals. (32) This trial assessed the effect of an intervention targeting physicians and their patients on rates of CRC screening (FOBT) in a US community setting. 94 community primary care physicians were randomly assigned to a control group or to an intervention group receiving an educational seminar and "academic detailing". 9,652 patients were enrolled for 2 years, and 3,732 patients were enrolled for 5 years. There was no increase in any CRC screening that occurred in the intervention group for patients enrolled for 2 years and 5 years (12.7% vs. 12.5%, p=0.51; 9.7% vs. 8.6%, p=0.45).

Question 3

We were not able to retrieve studies specifically aimed at investigating which quality indicators are currently used to evaluate the effectiveness of communicating information to the general public concerning CRC screening. We found no information on standardised quality checklists, or patient and health professional evaluation forms. We analysed the previously mentioned 25 RCTs in order to obtain a snapshot of the most widespread outcomes, considering that a change in the outcome measure (knowledge, attitude, behaviour) are indirect measures of the quality of an intervention. The most frequently reported outcome was rate of compliance/participation in the screening programme addressed by the informational campaign (17 out of 25 studies). (1-6, 9, 13-17, 20-23, 25) Participation rate was assessed through the analysis of medical charts, number of returned FOBT cards, or self-reported by the patients. Ten out of 25 RCTs reported knowledge outcomes, i.e. knowledge of screening programmes and techniques, CRC risk perception, screening risk perception, risk judgments, barriers' knowledge. (1, 7, 8, 10-12, 14, 18, 19, 24) Eight out of 25 RCTs reported attitude outcomes, i.e. intention to attend screening, positive and negative attitudes to screening, number of participants asking to attend a screening. (6-8, 14, 17, 22-24)

CONCLUSIONS

Question 1

Although we retrieved many RCTs assessing education programmes on CRC screening for patients and the general population it is difficult to draw definitive conclusions. The currently available strategies used for communicating information about CRC screening to the general public differ in terms of type of intervention, type of comparator (different definition of "usual care"), setting, and considered outcomes. Comparing tailored vs. non tailored communication strategies, tailored programmes were associated with a moderate increase in behaviour outcomes (i.e. participation rate) and a low influence on knowledge and attitude outcomes. More intense non tailored programmes appeared to increase knowledge, attitude, and behaviour even if for the latter outcome data are limited. Finally, when compared with usual care (no intervention, standard screening invitation and/or referral) both tailored and non tailored strategies improved knowledge, attitudes, and behaviour even if, again, data cannot be considered definitive.

Evidence on this topic comes from many RCTs which assure a high internal validity. However, the applicability of these results could be affected by the so-called volunteer bias: the sample population chosen may not be representative of the general population because trial participants are likely to have a higher health attitude, knowledge of screening programmes, and better life-expectancy than non participants. This could have led to an overestimation of treatment effects (LEVEL OF EVIDENCE I).

Question 2

Very limited data on education programmes targeting health professionals are available. One RCT involving 94 primary care physicians and more than 9000 patients showed no increase in participation in CRC screening (LEVEL OF EVIDENCE II).

Question 3

The most common reported outcome used to assessed the effectiveness of communicating information to the general public concerning CRC screening is compliance/participation rate. Knowledge and attitude outcomes were also assessed through a variety of questionnaires, which were very rarely standardised and validated. This precludes any attempt to compare results coming from different studies.

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Table 1: Studies' Summary: Tailored vs. Non Tailored Intervention

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	Attitude	Behaviour
Basch 2006	Urban minority N=456 (USA)	Tailored telephone educational programme	Mailed printed materials	-	-	Any type of CRC Screening within 6 months: RR=4.4, (95% CI 2.6-7.7)
Jerant 2007	General population, N=54 (USA)	Personally tailored interactive multimedia computer programs	Non-tailored version of the IMCP (electronic leaflet)	Estimated effect of experiment adjusted for baseline: Knowledge 0.02 (95% CI -1.82-1.87); p=0.978	Estimated effect of experiment adjusted for baseline: Readiness 5.01 (95% CI 1.13-22.23); p=0.034. Self-efficacy 0.23 (95% CI 0.00-0.46); p=0.049. Barriers -0.22 (95% CI -0.51-0.08); p=0.149. Benefits 0.08 (95% CI -0.12-0.27); p=0.445	-
Marcus 2005	Population referring to the Cancer Information Service N=4,014 (USA)	Single tailored (ST) or multiple mail out of print material (MR, MRT)	Single untailored (SU) mail out of print material	-	-	Response rate and screening rate (SU versus ST, MT, MRT combined): No significant difference across experimental conditions, either at 6 or 14 months follow-up
Miller 2005	General population, N=204 (USA)	Nurse counselling	Computer-assisted instruction	FOBT Knowledge Results: No significant difference	FOBT Attitude Results: No significant difference	Number of returned test kit at 1-month follow up No significant difference (p=0.89, χ2)
Myers 1991	Members of health insurance company, N=2,201 (USA)	Usual care plus a reminder telephone call, self-held screening booklet (ColoRecord), and a telephone call giving instructions in testing	An advance letter announcing a subsequent mailing of a colorectal cancer screening kit; 2) the screening kit, including a cover letter, three FOBTs, and information pages; 3) a mailed reminder for those who did not re- turn FOBTs within 15 days	-	-	FOBT compliance: significantly higher in the intervention groups. The most intensive intervention "package": 21% compliance increment compared to usual care

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	Attitude	Behaviour
Ruffin 2007	General population, N=174, (USA)	Colorectal Web: Interactive Web programme	Web programme with no interaction	-	-	Participants having any type of CRC screening 2 and 8 week follow up: No significant difference between groups 24 week follow up: participants in the intervention group were significantly (p=0.035) more likely to get screened for CRC than the control arm. No statistically significant difference between the study arms on type of CRC screening completed
Stokamer 2004	General population N=788 (primary care clinics USA)	2-page intensive patient information handout and a one-on-one 10- to 15-minute educational session on the importance of CRC screening and FOBT by a trained nurse	Standard patient education-enlarged version of the manufacturer's instructions	-	-	Proportion of patients who returned the FOBT cards: significantly higher in the intensive education group than with those who received standard education p<0.001

General population refers to people aged 50 year old or older at average risk for CRC

Table 2: Studies' Summary: Different Intensity of Non Tailored Intervention

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	**Attitude**	**Behaviour**
Brotherst one 2006	General population, N=318 general practice UK	Written leaflet with a set of illustrations	Written leaflet	Understanding of the preventive aim of FS OR = 3.75; CI: 1.16–12.09; p = 0.027	-	-
Dolan 2002	General population, N=96 (suburban Practice, USA)	2-part standardized interview including a detailed analysis of the decision options using the analytic hierarchy process	2-part standardized interview (no detailed analysis of the decision options using the analytic hierarchy process)	Decision process: patients in the intervention group had lower decisional conflict regarding CRC screening decisions (p=0.01) due to increased knowledge, better clarity of values, and higher ratings of the quality of the decisions they made.	No difference between the groups in the number of patients who planned screening tests	No difference between the groups in the number of patients who completed planned screening tests
Griffith 2008a*	General population, N=106 (USA)	Decision aid with an explicit discussion on the no screening option	Decision aid without an explicit discussion on the no screening option	Statistically significant increase in clarity of information on benefits and on downsides, amount of information on downsides, balance and overall rating	-	-
Griffith 2008 b*	General population, N=99 (USA)	5-option version of the decision aid	2-option decision aid	No significant difference in knowledge score (p=0.75), decisional conflict (p = 0.43), and decision satisfaction (p = 0.78)	No significant difference in screening interest (p=0.76), Test preferences (p = 0.11)	-
Lipkus 2005	Carpenters N=860, (USA)	Comprehensive information intervention (tailored and non tailored)	Basic information intervention (tailored and non tailored)	Knowledge of CRC risk factors was highest among participants who received tailored and comprehensive information at 3, 12, and 24 months post-baseline compared to the other groups. No significant difference was found for risk perceptions and worry.	-	Initial, yearly, and repeat FOBT screening: No statistically significant difference

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	Attitude	Behaviour
Lipkus 2006	General population, N=160 (USA)	Absolute risk condition only and absolute plus comparative risk condition	General information about CRC screening and risk factors	Comparative CRC risk: higher in the intervention groups. Perceived absolute risk did not vary by group.	Participants who received social comparison risk factor feedback expressed greater intentions to screen via a FOBT than participants who received absolute risk feedback and controls	-
Tilley 1999	28 worksites (more than 5000 participants) USA	Company-sponsored screening programme plus an enhanced health promotion programme	Usual care-Company-sponsored screening programme	-	-	Compliance confirmed by worksite documentation OR: 1.71 (95% CI 1.1-2.7); p=0.012 Coverage confirmed by worksite documentation OR: 1.57 (95% CI 1.2-2.0); p<0.001
Wolf 2000	Elderly population (≥65), N=399 (Primary care, USA)	Relative risk reduction (RRR) or absolute risk reduction (ARR) information script	brief description of FOBT and flexible sigmoidoscopy	-	Interest in undergoing screening and Intent to undergo screening: no significant difference	-

General population refers to people aged 50 year old or older at average risk for CRC

* Control trial (randomisation not performed)

Table 3: Studies' Summary: Tailored and Non Tailored Intervention vs. Usual Care

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	Attitude	Behaviour
Cole 2007	General population, N=2400 (Australia)	Different mail invitation strategies to a FIT based CRC screening (Advance notification, Risk, Advocacy)	Standard invitation-to-screen letter	-	-	Participation rate within 3 months: RR=1.23, (95% CI 1.06–1.43) Advance Notification vs Control group
Costanza 2007	General population, N= 2448 (USA)	Mailed print brochure and three months later a telephone counselling (TCC)	Usual care- no details	-	-	Frequency of completed test: No significant difference
Denberg 2006	Asymptomatic subjects referred to colonoscopy, N=781 (Ambulatory setting, USA)	Mailed print brochure	Usual care- written instructions to call the endoscopy laboratory to schedule a colonoscopy	-	-	Compliance with colonoscopy: difference in completion rate: 11.7% (95% CI, 5.1-18.4%) p=0.001
Hart 1997	General population, N=1571 (UK)	Leaflet	No leaflet	-	-	Compliance with screening: significant difference in men but not in women
Myers 2007	General population N=1546 urban practice (USA)	Mailed standard intervention (SI), tailored intervention (TI) group, and Tailored Intervention (TIP) group plus a phone reminder	Mailed standard intervention usual care	-	-	% Screening use (OR vs control group) Statistically significant for SI and TIP (p=0.003, p=0.001) Overall screening preference: no significant difference

Study ID	Population#	Intervention	Control	Outcome/Results		
				Knowledge	Attitude	Behaviour
Pignone 2000	General population, N=249, community primary care (USA)	11-minute educational video on CRC screening	Control video on car safety	-	CRC screening test ordered (according to chart review): Difference: 20.7 (8.6–32.9) Unadjusted Relative Risk for having a test ordered 1.79 (95% CI 1.23-2.58)	CRC screening test completed (according to chart review): Group difference: 14.2 (3.0–25.4)
Robb 2006 and 2008	General population, N=3365 General Practices (UK)	Risk factor group: leaflet on CRC risk factors; risk and screening group: leaflet on risk factor for CRC plus information on CRC screening.	No information leaflet;	Total knowledge score: significantly different (p=0.01). Anxiety mean, comparative perceived risk, absolute perceived risk: no significant difference	Interest in screening: no significant difference	-
Wardle 2003	FS Trial population, N=2966 (primary care UK)	Mailed pshyco-educational intervention (booklet) around 2-3 weeks before screening invitation	Usual screening invitation	-	Negative attitudes: lower in the intervention group; higher self efficacy for seeking social support in the intervention group Intention to screening: higher in the intervention group (p<0.001)	Attendance rate: 3.6% higher in the intervention group (p<0.05)
Zapka 2004	General population, N=938 (Primary care, USA)	Home-mailed video	Usual care	-	-	Sigmoidoscopy with or without any other test: OR: 1.22 (95% CI 0.88-1.70) Other test combination: OR: 0.84 (95% CI 0.63–1.14)

General population refers to people aged 50 year old or older at average risk for CRC

Table 4: Search Strategies

Search Strategies - CRC Patient Information Review

Medline 1996-2008 (15/09/2008)

	Searches	Results
1	exp Colorectal Neoplasms/	55787
2	(cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$).ti,ab.	704221
3	(colorectal$ or colon or rectal or rectum or bowel).ti,ab.	121862
4	((cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$) adj3 (colorectal$ or colon or rectal or rectum or bowel)).ti,ab.	45805
5	CRC.ti,ab.	3441
6	4 or 1 or 5	65973
7	exp Mass Screening/	55638
8	(screen$ or prevent$).ti,ab.	525031
9	(earl$ adj3 detect$).ti,ab.	22263
10	8 or 7 or 9	559642
11	6 and 10	11046
12	exp Decision Theory/ or exp Decision Making/ or exp Decision Support Techniques/	93117
13	exp Pamphlets/	1208
14	exp Counseling/	11513
15	exp Audiovisual Aids/	26363
16	exp Internet/	27006
17	exp Consumer Health Information/	159
18	((decision adj3 aid$) or (pamphlet$ or booklet$ or leaflet$ or brochure$ or PIL or handout$ or print$ or written or tape$ or video$ or audio$ or internet or computer$ or visual or multimedia or verbal$ or counsel$)).ti,ab.	297590
19	18 or 16 or 13 or 17 or 12 or 15 or 14	420147
20	exp Attitude to Health/ or exp Health Education/ or exp Health Educators/ or exp Health Promotion/ or exp Health Knowledge, Attitudes, Practice/	184489
21	exp Patient Education as Topic/ or exp Informed Consent/	45530
22	exp Consumer Satisfaction/	37077
23	((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or	2268880

	communit$ or population$ or informed or shared)).ti,ab.	
24	(decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent).ti,ab.	1342218
25	(((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$ or informed or shared)) adj3 (decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent)).ti,ab.	92868
26	25 or 22 or 21 or 20	266500
27	26 or 19	636427
28	27 and 11	1845
29	limit 28 to yr="2008"	130
30	from 29 keep 1-130	130
31	28	1845
32	limit 31 to yr="2007"	231
33	from 32 keep 1-231	231
34	28	1845
35	limit 34 to yr="2006"	218
36	from 35 keep 1-218	218
37	28	1845
38	limit 37 to yr="2005"	216
39	from 38 keep 1-216	216
40	28	1845
41	limit 40 to yr="2004"	172
42	from 41 keep 1-172	172
43	28	1845
44	limit 43 to yr="2003"	174
45	from 44 keep 1-174	174
46	28	1845
47	limit 46 to yr="2002"	139
48	from 47 keep 1-139	139
49	28	1845

50	limit 49 to yr="2001"	117
51	from 50 keep 1-117	117
52	28	1845
53	limit 52 to yr="2000"	147
54	from 53 keep 1-147	147
55	28	1845
56	limit 55 to yr="1999"	93
57	from 56 keep 1-93	93
58	28	1845
59	limit 58 to yr="1998"	64
60	from 59 keep 1-64	64
61	28	1845
62	limit 61 to yr="1997"	82
63	from 62 keep 1-82	82
64	28	1845
65	limit 64 to yr="1996"	62
66	from 65 keep 1-62	62

Medline 1988-1995 (15/09/2008)

	Searches	Results
1	exp Colorectal Neoplasms/	46445
2	(cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$).ti,ab.	585336
3	(colorectal$ or colon or rectal or rectum or bowel).ti,ab.	96798
4	((cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$) adj3 (colorectal$ or colon or rectal or rectum or bowel)).ti,ab.	21760
5	CRC.ti,ab.	339
6	4 or 1 or 5	50408
7	exp Mass Screening/	32755
8	(screen$ or prevent$).ti,ab.	328871
9	(earl$ adj3 detect$).ti,ab.	15468
10	8 or 7 or 9	354177

11	6 and 10	4130
12	exp Decision Theory/ or exp Decision Making/ or exp Decision Support Techniques/	37314
13	exp Pamphlets/	1200
14	exp Counseling/	13494
15	exp Audiovisual Aids/	42127
16	exp Internet/	2
17	exp Consumer Health Information/	0
18	((decision adj3 aid$) or (pamphlet$ or booklet$ or leaflet$ or brochure$ or PIL or handout$ or print$ or written or tape$ or video$ or audio$ or internet or computer$ or visual or multimedia or verbal$ or counsel$)).ti,ab.	224170
19	18 or 16 or 13 or 17 or 12 or 15 or 14	301064
20	exp Attitude to Health/ or exp Health Education/ or exp Health Educators/ or exp Health Promotion/ or exp Health Knowledge, Attitudes, Practice/	113158
21	exp Patient Education as Topic/ or exp Informed Consent/	33555
22	exp Consumer Satisfaction/	13565
23	((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$ or informed or shared)).ti,ab.	1792328
24	(decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent).ti,ab.	904300
25	(((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$ or informed or shared)) adj3 (decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent)).ti,ab.	46953
26	25 or 22 or 21 or 20	166433
27	26 or 19	447762
28	27 and 11	397
29	limit 28 to yr="1995"	66
30	from 29 keep 1-66	66
31	28	397
32	limit 31 to yr="1994"	33
33	from 32 keep 1-33	33
34	28	397

35	limit 34 to yr="1993"	38
36	from 35 keep 1-38	38
37	28	397
38	limit 37 to yr="1992"	36
39	from 38 keep 1-36	36
40	28	397
41	limit 40 to yr="1991"	24
42	from 41 keep 1-24	24
43	28	397
44	limit 43 to yr="1990"	33
45	from 44 keep 1-33	33
46	28	397
47	limit 46 to yr="1989"	31
48	from 47 keep 1-31	31
49	28	397
50	limit 49 to yr="1988"	12
51	from 50 keep 1-12	12

Embase 1988-2008 (15/09/2008)

	Searches	Results
1	exp COLORECTAL TUMOUR/ or exp COLORECTAL ADENOMA/ or exp COLORECTAL CARCINOMA/ or exp COLORECTAL CANCER/	44115
2	exp COLON ADENOCARCINOMA/ or exp COLON CANCER/ or exp COLON CARCINOMA/ or exp COLON ADENOMA/	73080
3	(cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$).ti,ab.	917603
4	(colorectal$ or colon or rectal or rectum or bowel).ti,ab.	162871
5	((cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$) adj3 (colorectal$ or colon or rectal or rectum or bowel)).ti,ab.	56276
6	CRC.ti,ab.	3611
7	6 or 1 or 2 or 5	88821
8	exp MASS SCREENING/ or exp SCREENING/ or exp CANCER SCREENING/ or exp SCREENING	159356

	TEST/	
9	(screen$ or prevent$).ti,ab.	648064
10	(earl$ adj3 detect$).ti,ab.	27938
11	8 or 10 or 9	728394
12	11 and 7	15140
13	exp PATIENT DECISION MAKING/ or exp DECISION MAKING/ or exp CLINICAL DECISION MAKING/ or exp DECISION THEORY/ or exp MEDICAL DECISION MAKING/ or exp DECISION SUPPORT SYSTEM/	91222
14	exp COUNSELING/ or exp PATIENT COUNSELING/	42160
15	exp Audiovisual Equipment/	28087
16	exp INTERNET/	27026
17	exp PATIENT INFORMATION/ or exp CONSUMER HEALTH INFORMATION/ or exp MEDICAL INFORMATION/	42681
18	((decision adj3 aid$) or (pamphlet$ or booklet$ or leaflet$ or brochure$ or PIL or handout$ or print$ or written or tape$ or video$ or audio$ or internet or computer$ or visual or multimedia or verbal$ or counsel$)).ti,ab.	368148
19	18 or 16 or 13 or 17 or 15 or 14	535075
20	exp ATTITUDE TO HEALTH/ or exp HEALTH EDUCATOR/ or exp HEALTH PROMOTION/	26014
21	exp PATIENT EDUCATION/ or exp HEALTH EDUCATION/	71035
22	exp INFORMED CONSENT/	17669
23	exp KNOWLEDGE/	4926
24	exp PATIENT SATISFACTION/	34083
25	exp PATIENT ATTITUDE/ or exp CONSUMER ATTITUDE/ or exp HEALTH PERSONNEL ATTITUDE/	111914
26	((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$ or informed or shared)).ti,ab.	2913672
27	(decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent).ti,ab.	1637878
28	(((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$ or informed or shared)) adj3 (decision$ or informat$ or educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$ or consent)).ti,ab.	103006
29	25 or 22 or 28 or 21 or 24 or 23 or 20	269720

30	19 or 29	741436
31	30 and 12	2226
32	limit 31 to yr="2008"	160
33	from 32 keep 1-160	160
34	31	2226
35	limit 34 to yr="2007"	264
36	from 35 keep 1-264	264
37	31	2226
38	limit 37 to yr="2006"	259
39	from 38 keep 1-259	259
40	31	2226
41	limit 40 to yr="2005"	262
42	from 41 keep 1-262	262
43	31	2226
44	limit 43 to yr="2004"	211
45	from 44 keep 1-211	211
46	31	2226
47	limit 46 to yr="2003"	203
48	from 47 keep 1-203	203
49	31	2226
50	limit 49 to yr="2002"	180
51	from 50 keep 1-180	180
52	31	2226
53	limit 52 to yr="2001"	127
54	from 53 keep 1-127	127
55	31	2226
56	limit 55 to yr="2000"	125
57	from 56 keep 1-125	125
58	31	2226
59	limit 58 to yr="1999"	69

60	from 59 keep 1-69	69
61	31	2226
62	limit 61 to yr="1998"	60
63	from 62 keep 1-60	60
64	31	2226
65	limit 64 to yr="1997"	66
66	from 65 keep 1-66	66
67	31	2226
68	limit 67 to yr="1996"	55
69	from 68 keep 1-55	55
70	31	2226
71	limit 70 to yr="1995"	42
72	from 71 keep 1-42	42
73	31	2226
74	limit 73 to yr="1994"	37
75	from 74 keep 1-37	37
76	31	2226
77	limit 76 to yr="1993"	25
78	from 77 keep 1-25	25
79	31	2226
80	limit 79 to yr="1992"	27
81	from 80 keep 1-27	27
82	31	2226
83	limit 82 to yr="1991"	14
84	from 83 keep 1-14	14
85	31	2226
86	limit 85 to yr="1990"	15
87	from 86 keep 1-15	15
88	31	2226
89	limit 88 to yr="1989"	13

90	from 89 keep 1-13	13
91	31	2226
92	limit 91 to yr="1988"	10
93	from 92 keep 1-10	10

PsychInfo 1988-2008 (15/09/2008)

	Searches	Results
1	(cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$).ti,ab.	22372
2	(colorectal$ or colon or rectal or rectum or bowel).ti,ab.	2860
3	((cancer$ or neoplas$ or tumour$ or tumour$ or adenoma$) adj3 (colorectal$ or colon or rectal or rectum or bowel)).ti,ab.	666
4	CRC.ti,ab.	204
5	3 or 4	755
6	exp SCREENING TESTS/ or exp SCREENING/ or exp CANCER SCREENING/ or exp HEALTH SCREENING/	12075
7	(screen$ or prevent$).ti,ab.	103370
8	(earl$ adj3 detect$).ti,ab.	2245
9	6 or 7 or 8	107948
10	5 and 9	353
11	exp READING/ or exp READING MATERIALS/	10190
12	exp AUDIOVISUAL COMMUNICATIONS MEDIA/	10542
13	exp COUNSELING/	42323
14	((decision adj3 aid$) or (pamphlet$ or booklet$ or leaflet$ or brochure$ or PIL or handout$ or print$ or written or tape$ or video$ or audio$ or internet or computer$ or visual or multimedia or verbal$ or counsel$)).ti,ab.	272727
15	11 or 12 or 13 or 14	306072
16	exp HEALTH EDUCATION/ or exp HEALTH PROMOTION/	14961
17	exp DECISION MAKING/ or exp DECISION THEORY/	34935
18	exp INFORMED CONSENT/	2378
19	exp HEALTH KNOWLEDGE/ or exp HEALTH ATTITUDES/ or exp CONSUMER SATISAFACTION/	8821
20	((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$)).ti,ab.	773213

21	(decision$ or informat$ educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$).ti,ab.	576709
22	(((service$ adj1 user$) or (patient$ or consumer$ or client$ or individual$ or personal$ or communit$ or population$)) adj3 (decision$ or informat$ educat$ or choice$ or prefer$ or priorit$ or value$ or aware$ or understand$ or knowledge or attitude$ or belief$)).ti,ab.	40422
23	16 or 17 or 18 or 19 or 22	93950
24	15 or 23	385329
25	10 and 24	150
26	limit 25 to yr="1988 - 2008"	148

10.1.2 Evidence tables

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Basch 2006	RCT	Intervention: tailored telephone educational programme (aimed at establishing a positive and trusting rapport with the recipient; reinforcing accurate knowledge and healthful beliefs, correcting misconceptions, and bolstering motivation to obtain a CRC screening on the basis of the participant's readiness and individual cognitive factors; addressing identified barriers and skill deficits that could impede CRC screening; providing social and emotional support for obtaining CRC screening; and eliciting a verbal commitment to obtain CRC screening. Emphasis was placed on positive reinforcement, enhancement of perceived self-efficacy to overcome barriers, and the message that there is support from scientists, medical doctors, and health organisations for recommended screening). Control: mailed printed materials (brochure published by the Centers for Disease Control and Prevention, which included information about CRC, how it can be prevented through early detection and treatment, the asymptomatic nature of the disease, descriptions of the various kinds of recommended screening tests, and a message to the reader to talk with his or her physician and to seek screening)	456 participants extracted from the membership lists of a health benefit fund older than 52 year old Between 2000-2003 USA (New York City metropolitan area)	6 months	Receipt of CRC screening (a 3-day faecal occult blood test-defined as 2 samples from each of 3 consecutive bowel movements - sigmoidoscopy, colonoscopy, or a barium enema) within 6 months of randomisation	***Participants received screening for CRC within 6 months of randomisation*** intervention group n=61 (27%) (29 had a 3 day faecal occult blood test, 29 had a colonoscopy, 2 had a flexible sigmoidoscopy, and 1 had a 3- day faecal occult blood test followed by a colonoscopy) control group: n=14 (6.1%) (13 had a colonoscopy and 1 had a 3-day faecal occult blood test followed by a sigmoidoscopy) ***Absolute screening rate difference*** 20.9% (14.34-27.46) ***Relative risk*** 4.4 (95% CI 2.6-7.7) There was an intervention effect within each of the subgroups (gender, age, education, marital status, income)	**II** Telephone outreach can increase the rate of CRC screening in an urban minority population with a large magnitude of effect compared with the mailed information, as measured by relative risk estimates or differences between groups in the proportion of the population screened. The intervention effect was consistent for all the demographic subgroups examined. Despite the increase in recommended screening in the intervention group, a large percentage did not receive screening within the 6-month window, even after tailored telephone outreach.

Quality assessment: randomisation by blocks according to sex and age; 7.3% of the screened population was randomised (35.6% not interested, 57.1% interested but not eligible); adequate randomisation procedure (table of random permutations); unclear allocation concealment; blinding of participants not applicable but a blinded ascertainment of outcomes was conducted; no information on contamination bias protection; unplanned interim analysis (50% of the sample size): trial stop for early benefit.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Brotherstone 2006	RCT	Recommended screening: flexible sigmoidoscopy (FS) Intervention: written leaftet accompanied with a set of illustrations showing the development of cancer from polyps and removal of polyps during flexible sigmoidoscopy Control: written leaftet alone	318 people, aged 60–64 invited to participate Setting: general practice London, UK 123/318 (38.7%) were randomly selected for the telephonic interview	Not reported	Primary: understanding of the preventive aim of FS assessed by a structured telephonic interview and correlation with age, gender, and socioeconomic status (Townsend score) Secondary: screening attendance rate	***Interviews completed*** Overall: 65/123 (52.8%) Intervention: 30 Control: 35 ***Understanding of the preventive aim of FS*** OR = 3.75; CI: 1.16–12.09; p = 0.027 This trend remained significant controlling for age, gender and Townsend scores (OR = 10.85; CI: 1.72–68.43; p = 0.011). ***Attendance rate calculated on the randomised sample (N=318)*** Intervention: 68.3% Control: 67.5% difference not statistically significant	**II** People who were sent the illustrations were significantly more likely to understand that the aim of FS screening was to detect polyps and prevent cancer rather than just to detect cancer.

Quality assessment: unclear randomisation and allocation concealment; no information on the analysis; no information on protection against contamination bias (overall: very low quality).

Author publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Cole 2007	RCT	Four CRC screening invitation strategies: (a) Control: standard invitation-to-screen letter explaining risk of CRC and the concept, value and method of screening; (b) Risk: invitation with additional messages related to CRC risk; (c) Advocacy: invitation with additional messages related to advocacy for screening from previous screening programme participants (d) Advance Notification: first, a letter introducing control letter messages followed by the standard invitation-to-screen. Invitations included an FIT kit.	2,400 people aged 50–74 years selected from the electoral roll of the Australian Electoral Commission Between 17 January and 7 April 2005 Community screening programme Adelaide, South Australia.	12 weeks	Primary: participation in screening within 12 weeks from the date of invitation compared to control Secondary: early and late participation (at week 2 and 14)	***Participation at week 12*** Control group 237/600 (39.5%) Advance Notification group 290/600 (48.3%) *Advance Notification group vs Control group* RR=1.23, 95% CI 1.06–1.43 Risk group 242/600 (40.3%) No statistically significant increase versus control group Advocacy group 216/600 (36.0%) No statistically significant increase versus control group ***Participation at week 2 (early participation)*** Advance Notification group vs Control group RR=1.23, 95% CI 1.06–1.43 ***Participation at week 14*** Advance Notification group vs Control group RR 1.38, 95% CI 1.11–1.73	II Advance Notification group vs had a significantly increased participation rate compared with the Control group at week 12

Quality assessment: unclear randomisation and allocation concealment; no information on the type of analysis; No information on contamination bias protection; (overall: very low quality).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Costanza 2007	RCT	Recommended screening: annual FOBT and sigmoidoscopy every 5 years or colonoscopy every 10 years Intervention: two-stepped intervention: a mailed print brochure (three colour-coded sections, "what is CRC", "Are you at risk", expert recommendation). Three months later a telephone counselling (TCC) consisting in a computer assisted interviewing technique. Control group: usual care	2,806 participants identified from data in UMass Health Care system (UMMHC) administrative databases, aged 50 and 75 years old Between 2001 and 2004 Primary care setting USA	Chart audits were completed between 17 and 22 months after a subject's baseline survey mailing.	Frequencies of completed tests in the intervention and usual care arms assessed through the analysis of a chart audit of the medical records of participants	***Number of available medical records*** Intervention: 1187 Control: 1261 ***Frequency receipt of CRC screening tests in each study period by study group*** ***FOBT*** Intervention No test post brochure: 1084 (88%) Between brochure and TCC: 30 (3%) Post TCC: 109 (9%) Control No test post brochure: 1131 (90%) Between brochure and TCC: 24 (2%) Post TCC: 106 (8%) p=0.44 ***Sigmoidoscopy*** Intervention No test post brochure: 1181 (99%) Between brochure and TCC: 1 (<1%) Post TCC: 5 (<1%) Control No test post brochure: 1252 (99%) Between brochure and TCC: 4 (<1%) Post TCC: 5 (<1%) p=not calculated ***Colonoscopy*** Intervention No test post brochure: 1017 (86%) Between brochure and TCC: 30 (3%) Post TCC: 140 (12%) Control No test post brochure: 1075 (85%) Between brochure and TCC: 35 (3%) Post TCC: 150 (12%) p=0.93	**II** This study showed no difference in screening rates between intervention and control arms

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Any test <u>Intervention</u> No test post brochure: 888 (75%) Between brochure and TCC: 61 (5%) Post TCC: 238 (20%) <u>Control</u> No test post brochure: 962 (76%) Between brochure and TCC: 63 (5%) Post TCC: 236 (19%) p=0.68	

Quality assessment: unclear randomisation and allocation concealment; 17.5% of randomised participants excluded at the baseline survey (similar exclusion rate in the two groups; reasons for exclusion fully reported); intention to screen analysis; record audits available for 87% of the randomised population; no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Denberg 2006	RCT	Recommended screening: colonoscopy Intervention: home mailed brochure (1-page, 2-sided brochure reporting reasons for non compliance with screening, lifetime risk for CRC for men and women at average risk; the concept of cancer prevention-finding and removal of benign polyps that might develop into cancer-as well as early detection of cancer; the typically asymptomatic nature of polyps and early-stage cancer; how screening may help prevent death; a description of colonoscopy, including the use of conscious sedation to minimize discomfort; risk of colon perforation, colonoscopy discomfort; FOBT and sigmoidoscopy as alternatives to colonoscopy) Control: usual care (written instructions to call the endoscopy laboratory to schedule a colonoscopy)	781 asymptomatic 50 year old or older subjects who received referrals for screening colonoscopy Ambulatory setting Between February and November 2005 Colorado (USA)	4 months	Compliance with colonoscopy referrals assessed by records claims	***Compliance with colonoscopy referrals:*** Intervention: 70.7% Control: 59.0% 11.7% (95% CI, 5.1-18.4%) p=0.001 In the multivariate model, patients receiving a mailer were 20% more likely to complete colonoscopy than those patients not receiving a mailer.	**II** Patients referred for screening colonoscopy were substantially more likely to complete a procedure after receiving an inexpensive, mailed brochure that included a description of the procedure and a reminder to schedule an examination.

Quality assessment: adequate randomisation (random number generator); unclear allocation concealment; intention to treat analysis; no patients exclusion; no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Dolan 2002	RCT	Intervention: 2-part standardized interview: preliminary phase (brief description of CRC and the purpose of the study, a demographic survey, questions regarding family and personal history) and a 2nd part consisted of a detailed analysis of the decision regarding the recommended CRC options using the analytic hierarchy process with integration of quantitative data with less tangible, qualitative considerations such as values and preferences. Control: 2-part standardized interview: preliminary phase as in the intervention group and an educational phase (a short-470-word-description of CRC and the 5 screening programs for average risk patients recommended by the multidisciplinary expert panel- annual faecal occult blood tests, flexible sigmoidoscopy every 5 years, combined annual faecal occult blood tests and flexible sigmoidoscopy every 5 years, double contrast barium enema every 5 years, and colonoscopy every 10 years)	96 patients at average risk for colon cancer being seen for routine appointments Setting: suburban practice USA		Primary: decision process and decision outcomes measured by the decisional conflict scale (16-item scale designed to measure the amount of uncertainty a person has regarding a course of action and the factors contributing to the uncertainty). Secondary: complete screening plans	***Completition of the decisional conflict scale*** Overall: 78/96 (82%), Control: 37 Intervention: 41 Cronbach's alpha: 0.97. ***Mean decisional conflict scores*** Control: 1.83 Intervention: 2.03 Difference statistically significant when the effects of the physicians are controlled for in the analysis of variance, F ratio = 6.47, P =0.01 ***Decision outcome results*** Annual faecal occult blood tests Overall: chosen 40 (45%); completed 17 (43%) Control: chosen 17 (39%); completed 6 (35%) Intervention: chosen 23 (51%); completed 11 (48%) No test (wait & see) Overall: chosen 24 (28%); completed 23 (96%) Control: chosen 16 (37%); completed 15 (94%) Intervention: chosen 8 (18%); completed 8 (100%) Annual faecal occult blood tests and flexible sigmoidoscopy every 5 years Overall: chosen 14 (16%); completed 9 (64%)	II After controlling for the effects of the physicians in a factorial analysis of variance, patients who used the decision aid had lower decisional conflict regarding colorectal cancer screening decisions (F ratio 6.47, P = 0.01) due to increased knowledge, better clarity of values, and higher ratings of the quality of the decisions they made. There was no difference between the groups in decision outcomes. A multicriteria-based patient decision aid for decisions regarding CRC improved patient decision-making process but had no effect on decision implementation. No statistically significant difference between groups was found but a strong trend toward more patients choosing active screening tests in the experimental group was observed

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Control: chosen 8 (18%); completed 7 (88%) Intervention: chosen 6 (13%); completed 2 (33%) Flexible sigmoidoscopy every 5 years Overall: chosen 8 (9%); completed 5 (63%) Control: chosen 2 (5%); completed 1 (50%) Intervention: chosen 6 (13%); completed 5 (63%) Double contrast barium enema every 5 years Overall: chosen 1 (1%); completed 0 Control: chosen 0; completed 0 Intervention: chosen 1 (2%); completed 0 Colonoscopy every 10 years Overall: chosen 1 (1%); completed 1 (100%) Control: chosen 0; completed 0 Intervention: chosen 1 (2%); completed 1 (100%) No difference between the groups in the number of patients who completed planned screening tests: 14 (52%) of 27 in the control group and 18 (49%) of 37 in the experimental group, P = 1.0.	

Quality assessment: adequate randomisation (computer random number generator); unclear allocation concealment (separate randomisation schedules for each participating physician); factorial analysis of variance with 2 factors: physician and study group. 2/96 patients were excluded.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Griffith 2008a	CT	35 minute-decision aid about CRC screening. Intervention: decision aid includes a video segment of two men, one of whom decided against being screened Control: no explicit discussion on the no screening option Both versions first introduced the topics of colon cancer and screening. Introductory material also discussed lifetime colon cancer mortality risk with and without screening and how screening tests help detect colon cancer.	106 participants (mean age 60, range 50–81) recruited from three different sites United States	Not reported	Primary: subjective measures of decision aid content such as clarity and balance, and our secondary measures included knowledge and interest and intent to be screened. Secondary: overall impression of the decision aids	*Clarity of information on benefits* Intervention: 3.4 Control: 4.0 p<0.01 *Amount of information on benefits* Intervention: 2.9 Control: 2.9 p=0.72 *Clarity of information on downsides* Intervention: 3.2 Control: 3.6 p=0.03 *Amount of information on downsides* Intervention: 2.7 Control: 3.0 p=0.02 *Helped me sort what was important* Intervention: 3.5 Control: 3.8 p=0.13 *Helped me prepare for making a decision* Intervention: 3.5 Control: 3.9 p=0.03 *Balance* Intervention: 1.8 Control: 1.6 p=0.05 *Overall rating of video* Intervention: 3.5 Control: 3.8 p=0.03	III Including an explicit discussion of the option of "no screening" appears to increase the impression of "balance" away from strongly favouring screening but decreases the impression of clarity and overall rating, without large effects on screening interest, intentions, or knowledge.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Interest in screening <u>Intervention:</u> 3.4 <u>Control:</u> 3.5 p=0.54 ***Intent to be screened*** <u>Intervention:</u> 2.9 <u>Control:</u> 2.8 ,p=0.65	

Quality assessment: non random assignment of treatment based on gender and availability of the participants on scheduled focus group dates.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Griffith 2008b	CT	Screening options: FOBT, sigmoidoscopy, a combination of FOBT and sigmoidoscopy, colonoscopy, and barium enema. Intervention: 5-option version of the decision aid including FOBT, sigmoidoscopy, a combination of FOBT and sigmoidoscopy, colonoscopy, and barium enema. The decision aid contained introductory information about colon cancer and the screening decision, more detailed information about each of the tests, and comparative information for those who wished to decide between different tests. Control: 2-option decision aid, a shortened (approximately 15 minutes total content) version of the full decision aid that included only the two options, FOBT and colonoscopy Both versions first introduced the topics of colon cancer and screening. Introductory material also discussed lifetime colon cancer mortality risk with and without screening and how screening tests help detect colon cancer.	99 adults ages 48–75 not currently up-to-date with CRC screening (FOBT within the last year, sigmoidoscopy or barium enema in the last 5 years, colonoscopy within the last 10 years) USA	Not reported	Primary: differences in screening interest and patient test preferences between versions of the decision aid assessed by questionnaires Secondary: knowledge, decision satisfaction, and decisional Conflict	***Screening interest*** Intervention: 1.8 Control: 1.9 p = 0.76 ***Test preferences*** Intervention: 68% Control: 46% p = 0.11 ***Knowledge scores*** Intervention: 2.1 Control: 2.0 p = 0.75 ***Decisional conflict*** mean 1.9 in each group p = 0.43 ***Decision satisfaction*** mean 25 in each group p = 0.78	**III** No significant differences in terms of screening interest, patient test preferences, knowledge, decision satisfaction, and decisional conflict between the two versions of the decision aid were found. Thus, the number of test options has no major effect on interest in CRC screening.

Quality assessment: non random assignment of treatment based on gender and availability of the participants on scheduled focus group dates; no power calculation.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Hart 1997	RCT	Recommended screening: faecal occult blood test <u>Intervention:</u> leaflet about CRC screening explaining the high frequency of CRC and adenomatous polyps, the beneficial effects of polypectomy and the asymptomatic nature of the lesions <u>Control:</u> no leaflet	1,571 residents of Market Harborough aged 61 to 70 years UK	Not reported	Compliance with screening (number of subjects who completed faecal occult blood kit)	***Overall compliance with screening*** 513/1571 (33%) <u>Intervention:</u> 288/806 (35.7%) <u>Control:</u> 225/765 (29.4%) P=not reported <u>Men</u> 61-65y: intervention 36% (72/199), control 27% (52/194), p<0.05 66-70 y: intervention 39% (71/182), control 23% (39/166), p<0.01 <u>Women</u> 61-65y: intervention 38% (79/209), control 36% (67/186), p: NS 66-70y: intervention 31% (66/216), control 31% (67/219), p: NS	II The main finding of this study was that a health education leaflet could significantly increase compliance in men but not women.

Quality assessment: unclear randomisation and allocation concealment; no information on the analysis; no information on contamination bias protection; (overall: very low quality).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Jerant 2007	RCT	Intervention: personally tailored (to patient CRC screening preference, self-efficacy, perceived barriers, and stage of readiness) Interactive multimedia computer programs (IMCP) to encourage people not "up to date" for CRC screening to undergo screening via their preferred method. The tailored messages were a specific recommendation regarding CRC screening, generated by weighing subjects' responses to the CRC screening method preference item and, secondarily, to the stage of readiness, self-efficacy, perceived barriers, and prior CRC screening behaviours questions. Control: non-tailored version of the IMCP (electronic leaflet) with the same basic text, graphical, and animated guide information regarding potential risks, benefits, harms, and inconveniences of CRC screening as contained in experimental tailored IMCP (the manner in which information was presented differed between experimental and control IMCPs)	54 participants aged ≥50 Setting: University of California Davis Primary Care Network August 2005 through March 2006 USA	Not reported	Primary: CRC screening knowledge self-efficacy, perceived benefits and barriers, and stage of readiness	***Unadjusted primary outcomes*** ***Self-efficacy (S.D.)*** Control: 2.31 (0.55) Intervention: 2.60 (0.38) p=0.059 ***Barriers (S.D.)*** Control: 3.79 (0.60) Intervention 3.55 (0.54) p=0.145 ***Benefits (S.D.)*** Control: 1.88 (0.62) Intervention: 2.06 (0.45) p=0.260 ***Knowledge (S.D.)*** Control: 8.28 (2.72) Intervention: 8.83 (2.97) p=0.500 ***Readiness*** p=0.150 ***Estimated effect of experiment adjusted for baseline self-efficacy, barriers, benefits, knowledge, and readiness*** ***Self-efficacy*** 0.23 (95% CI 0.00-0.46); p=0.049 ***Barriers*** -0.22 (95% CI -0.51-0.08); p=0.149 ***Benefits*** 0.08 (95% CI -0.12-0.27); p=0.445 ***Knowledge*** 0.02 (95% CI -1.82-1.87); p=0.978 ***Readiness*** 5.01 (95% CI 1.13-22.23); p=0.034	II This study showed that a personally tailored IMCP was significantly more effective in bolstering CRC screening self-efficacy and increasing readiness to undergo CRC screening compared to a non-tailored "electronic leaflet" control IMCP. Moreover, a non-significant trend toward fewer perceived barriers to CRC screening for experimental subjects as compared with control. Finally, CRC screening knowledge increased equally in both groups.

Quality assessment: adequate randomisation (computer randomisation); unclear allocation concealment; 53% of the screened population was not randomised; 54/116 (47%) eligible participants agreed the randomisation (reasons fully described); no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Lipkus 2005	RCT	Recommended screening: FOBT Factorial 2x2 design: <u>Basic information intervention</u>: one set of interventions emphasized only basic risk factor information (age, family history, and polyps); <u>Comprehensive information intervention:</u> the other set emphasized a more comprehensive set of risk factors including lifestyle and occupational factors, Both interventions were delivered in a tailored (print plus phone) and non tailored (only print) fashion Primary comparison is tailored comprehensive information vs. non tailored basic information intervention	4292 (Randomised: 860) employed and retired carpenters between the ages of 50 and 75 receiving health care benefits through the New Jersey Carpenters Fund from 1996 to 1998. USA	3-month, and 1- and 2- year	Initial, yearly, and repeat FOBT screening Perceptions of absolute risk Knowledge of CRC risk factors Perceptions of comparative risk Negative emotions about getting CRC Basic, lifestyle, and occupational risk factors	The 3-,12-, and 24-month follow-up surveys were completed by 704, 658, and 615 participants ***FOBT screening rates by intervention group*** <u>Basic Non-tailored (%)</u> Year 1: 54 Year 2: 41 Year 3: 30 Repeat years 1–2: 38 Repeat years 2–3: 28 Repeat years 1–3: 28 <u>Basic Tailored (%)</u> Year 1: 61 Year 2: 43 Year 3: 35 Repeat years 1–2: 4 Repeat years 2–3: 28 Repeat years 1–3: 27 <u>Comprehensive Non-tailored (%)</u> Year 1: 57 Year 2: 41 Year 3: 44 Repeat years 1–2: 35 Repeat years 2–3: 32 Repeat years 1–3: 29 <u>Comprehensive Tailored (%)</u> Year 1: 64 Year 2: 44 Year 3: 36 Repeat years 1–2: 42 Repeat years 2–3: 31 Repeat years 1–3: 30	**II** Initial, yearly, and repeat screening was not affected by receipt of basic versus comprehensive information, tailoring, or their interaction, with two exceptions: first, participants in the tailored comprehensive group had the highest screening rate in year 1 than any other groups. Second, in year 3 (36 months post-baseline), participants who received the comprehensive non-tailored information had higher yearly screening rates than the other three groups.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Knowledge of CRC risk factors was highest among participants who received tailored and comprehensive information at 3, 12, and 24 months post-baseline compared to the other groups. No significant difference was found for risk perceptions and worry.	

Quality assessment: unclear randomisation and allocation concealment; 860 participants (20% of the 4292) were randomised (reasons fully reported). Despite random assignment, there were some significant between-group differences at baseline. Intent to treat analysis.

Author, publication year	Study design	Intervention	Participants	Outcome	Results	Level of evidence Conclusions
Meade 1994	RCT	Experimental 1: booklet with information on signs and symptoms of colon cancer, early detection of colon cancer.N.370 Experimental 2. Videotape. Content of the videotape mirrored that of the booklet. The videotape was 7½ minutes in length, which approximated the time required to read the booklet. N.374 Control: no intervention. N: 356	1100 participants 50 years or older, with ability to speak and read English, absence of visual and hearing impairments, ability to give free consent, and eligibility for at least one colon cancer screening measure within the recommended interval. USA	knowledge	Score improvement in knowledge (post-pre/pre) Booklet: 23% Video: 26% Control: 3% (P:0.05) No statistically significant difference was noted between the booklet and videotape groups.	**II** Both printed and videotaped materials enhanced colon cancer knowledge among patients with limited literacy skills. The inference from our data should be viewed with caution because only short-term knowledge recall was evaluated. Future studies will be required to determine how long this knowledge is retained and its effect on attitudinal and behavioural outcomes.

Quality assessment: randomisation by permuted blocks; adequate randomisation procedure (table of random permutations); unclear allocation concealment; blinding of participants not applicable but a blinded ascertainment of outcomes not clear; no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Marcus 2005	RCT	Recommended screening: any type CRC screening (faecal occult blood test [FOBT], flexible sigmoidoscopy, or colonoscopy) Four experimental conditions were compared: (1) control group: a single untailored (SU) mail out of print material; (2) a single tailored (ST) mail out of print material; (3) four (multiple) tailored (MT) mail outs of print materials spanning 12 months, all of which were tailored to information obtained at baseline; (4) four (multiple) re-tailored (MRT) mail outs also spanning 12 months, with re-tailoring of the print materials (mail outs 2, 3, and 4) based on updated information obtained from the 6-month follow-up interviews.	N=4,014 English-speaking people referring to the Cancer Information Service (CIS) of the National Cancer Institute (NCI) older than 50 year old 83% female USA	6-14 months	Primary: adherent or not adherent to CRC screening guidelines at each follow-up interview. Compliance was defined as receiving an FOBT, flexible sigmoidoscopy, or colonoscopy either at 6 months follow-up (among those who were nonadherent at baseline) or at 14 months follow-up (all participants). Secondary: interactions between the intervention and age (50–60 vs. other), race=ethnicity (White vs. other), education (some college or higher vs. other), and gender, as well as CRC screening history (never vs. ever at baseline).	***Response rate at 6-months*** 68% (n= 2,740), ***Response rate at 14-months*** 55% (n = 2,224) No significant difference across experimental conditions, either at 6 or 14 months follow-up ***Proportion adherent for CRC screening at baseline at 6 months follow-up (SU versus ST, MT, MRT combined)*** SU: 22% ST, MT, and MRT combined: 26% p=0.12 No significant differences by experimental condition within subgroups examined for moderator effects ***Proportion adherent for CRC screening at baseline at 14 months follow-up by experimental condition*** <u>All participants</u> Baseline: 0.20 SU: 0.42 ST: 0.44 MT: 0.51 MRT: 0.48 Trend: 0.03 p=0.05 Significant trend in the predicted direction for females (p=0.008), those with some history of screening (p=0.02), and in the 50–60 age group (p=0.006)	**II** A significant linear trend across the SU, ST, MT, and MRT groups was found at 14 months (42%, 44%, 51%, and 48%, respectively, p=0.05). Only for MT was there a significant difference compared with SU (p=0.03) for the sample as a whole, while no differences were found for MT vs. MRT at 14 months. Significant moderator effects in the predicted direction were found among females, younger participants, and among those with a history of CRC screening. Thus, the MRT intervention failed to show added benefit beyond the MT intervention, the significant intervention effects involving the MT and MRT conditions can be explained by tailoring and/or the longitudinal nature of both interventions. The most compelling evidence in support of tailoring was found for the ST condition among younger participants, where a significant need for interventions exists at the national level.

Quality assessment: unclear randomisation and allocation concealment; no information on the type of analysis; trained interviewers; the baseline interview completion rate was 67% (n=4,014); no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Miller 2005	RCT	Recommended screening: faecal occult blood screening (FOBT) Intervention: Computer-assisted instruction: educational multimedia computer program to teach patients about FOBT screening (a 2-minute segment on the incidence of CRC and the rationale for screening followed by an explanation on the screening process, including necessary dietary and medication modifications, procedures for sample collection, and sample mailing. The educational message was delivered by using a variety of computer animations, digital photographs, audio clips of clinic personnel's voices, and digital video segment) Control: nurse counselling (standardized to the printed instructions but not monitor): an office nurse met with each patient in a private setting to teach them how to complete the FOBT kit. Specific topics included dietary and medication restrictions, proper sample collection technique, and sample mailing.	204 patients enrolled among patients aged 50 years and older who were offered FOBT screening by their providers Setting: community-based Internal Medicine outpatient practice July 2001-April 2002 USA	1 month	Primary: compliance with FOBT screening measured by the return of the test kit within 30 days of distribution as defined by postmark Secondary: measures of patients' knowledge of the screening procedure and their attitudes toward CRC screening as assessed by a post intervention questionnaire	***Number of returned test kit at 1-month follow up*** Control: 64/101, (63%) Intervention: 58/93 (62%) 95% CI for difference: -15%-113%, p=0.89, χ^2). ***FOBT Knowledge and Attitude Results n (%)*** Completed follow-up survey Control: 71 (70) Intervention: 63 (68) Questions (n=6) answered correctly, mean (SD) Control: 4.1 (1.1) Intervention: 4.3 (1.3) Self-reported intent to comply with annual FOBT • Less likely than baseline Control: 24 (34) Intervention: 18 (29) • Same as baseline Control: 33 (47) Intervention: 34 (54) • More likely than baseline Control: 13 (19) Intervention: 11 (17) Perceived risk of CRC • Very low/low Control: 27 (39) Intervention: 30 (50) • Average Control: 32 (46) Intervention: 18 (30) • High/very high Control: 11 (16) Intervention: 12 (20)	**II** An educational multimedia computer program was as effective as nurse counselling, resulting in similar FOBT completion rates and a trend towards higher knowledge scores. In addition, our computer-based intervention was easily incorporated into routine office visits and was accessible to computer-naive, relatively uneducated patients.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						Utility of FOBT for early detection • Not useful/a little/moderately Control: 12 (18) Intervention: 9 (15) • Quite a bit Control: 25 (37) Intervention: 17 (29) • Extremely useful Control: 31 (46) Intervention: 33 (56) None was statistically significant	

Quality assessment: adequate randomisation and allocation concealment (permuted blocks with block randomisation scheme kept in a computerized data file inaccessible to the research assistant); blinded assessment of outcomes; 194/204 (9.7%) of the randomised population were excluded (reasons fully reported).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Myers 1991	RCT	Recommended screening: FOBT Four groups: Treatment Group 1 (n = 450): usual care plus a reminder telephone call (reminder call) at 30-days if no tests were returned. Treatment Group 2 (n = 450): usual care with the addition of a self-held screening booklet (ColoRecord) included in the screening kit and the 30-day reminder telephone call. Treatment Group 3 (n = 700): usual care, the ColoRecord booklet, the 30 day reminder call, and a telephone call giving instructions in testing (instruction call) within a week of screening kit mailing (this telephone survey was administered to 250 Group 3 subjects). Control Group (n=601): "usual care," that is: 1) an advance letter announcing a subsequent mailing of a colorectal cancer screening kit; 2) the screening kit, including a cover letter, three FOBTs, and information pages; 3) a mailed reminder for those who did not re- turn FOBTs within 15 days.	2,201 men and women aged 50 to 74 members of U.S. Healthcare, Inc. 53% men mean age 58 years USA April-July 1989	3 months	Primary: compliance with screening measured as the subjects who re-turned FOBTs within 90 days of kit mailings	*FOBT compliance* Overall: 837/2201 (38%) Control: 27% Treatment Group 1: 37% Treatment Group 2: 37% Treatment Group 3: 48% Differences among the four study groups were statistically significant (χ^2=59.15, p<0.001) Treatment Group 1 vs control: χ^2=11.1, p<0.005 Treatment Group 2 vs control: χ^2=11.6, p<0.005 Treatment Group 3 vs control: χ^2=58.4, p<0.001 Treatment Group 3 vs Treatment Group 1: χ^2=13.5, p<0.005 Treatment Group 3 vs Treatment Group 2: χ^2=12.9, p<0.005	**II** Findings related to overall treatment effect in the study sample showed that adher- ence increased by 10% when a reminder call (Group 1) was added to usual care (Control Group). Addition of the ColoRecord booklet (Group 2) did not appear to have any impact. Subject exposure to the most intensive intervention "package" (Group 3) was associated with a relatively large compliance increment (21%) in comparison to usual care

Quality assessment: unclear randomisation and allocation concealment (despite random assignment, the groups were found to differ in terms of age (χ^2=29.4, p=0.001). No information on the type of analysis.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Myers 2007	RCT	Four groups: (1) Standard Intervention (SI) group: received a mailed standard intervention (ie, a mailed CRC screening invitation letter, informational booklet, an SBT, and reminder letter). The screening invitation letter was personalized, encouraging recipients to return the completed FOBT and to call the practice and schedule FS screening. Detailed instructions concerning arranging FS screening were provided by a designated practice coordinator at the time of patient contact (2) Tailored Intervention (TI) group: standard intervention, plus 2 tailored "message pages." These pages included brief messages addressing personal barriers to FOBT and FS screening that were identified through analyses of baseline survey data. (3) Tailored Intervention plus reminder Phone call (TIP) group: standard intervention and the tailored message pages in which they were also designated to receive a reminder telephone call. During the call, a trained health educator reviewed the mailed materials and encouraged participants to consider screening. (4) Control group: usual care	1,546 participants (67% female) Setting: Jefferson Family Medicine Associates (JFMA), a large urban practice (1 central practice site at which 29 faculty physicians, 27 residents, and 8 fellows saw patients concurrently) November 2001 March 2002 USA	12 and 24 months	Primary: Screening use defined as having had ≥1 documented FOBT of any type or a self reported or documented FS, colonoscopy, or DCBE X-ray procedure performed during the 24-month observation period after random assignment to study group Overall screening preference	*% Screening use (OR vs control group)* Control (N=387): 32.56% SI (N=387): 45.74% OR: 1.68 (95% CI 1.25-2.53); p=0.001(raw); p=0.003 (adj) TI (N=386): 43.78% OR: 1.58 (95% CI 1.18-2.12); p=0.002 (raw); p=0.10 (adj) TIP (N=386): 48.45% OR: 1.91 (95% CI 1.42-2.56); p<0.001 (raw); p=0.001(adj) *Overall screening preference* TI vs SI OR: 0.94 (95% CI 0.71–1.25); p=0.683 (raw); p=0.683 (adj) TIP vs SI OR: 1.14 (95% CI 0.86–1.51); p=0.372 (raw); p=0.683 (adj) TIP vs TI OR: 1.21 (95% CI 0.91–1.61); p=0.193 (raw); p=0.580 (adj)	II CRC screening use was significantly higher in all intervention groups compared with the control group. These findings provide support for the use of at least a targeted intervention in primary care practice settings to increase the use of CRC screening among adult patients who are not up to date with CRC screening guidelines. With regard to the use of tailored interventions, we determined that screening did not differ significantly among the intervention groups. It is premature to conclude that the reminder calls had little impact on screening due to the finding that the reminder call was not delivered to a sizable proportion of participants in the TIP Group.

Quality assessment: non random assignment of treatment based on gender and availability of the participants on scheduled focus group dates; 1608/2579 (62%) of the eligible participants were randomised; intention to treat analysis.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Pignone 2000	RCT	Intervention: 11-minute educational video on colon cancer and then patients has to choose one of three colour-coded, patient-directed brochures to indicate their interest in screening (green: current readiness to be screened, yellow: some interest in screening but a need for additional discussion or information, red: no interest in screening at that time) Control: a video of similar length on car safety, seat belt use, and airbags and received a standard brochure on automobile safety.	249 consecutive patients between 50 and 75 years of age who had scheduled visits during the study period at the three practices. community primary care practices in two small to moderate-sized cities May to November 1998 USA	3 months	Differences in the proportions of patients in whom any CRC screening test (home FOBT, flexible sigmoidoscopy; or both) was ordered and completed (self reported and according to chart review) Change in participants' intent to ask their provider for a screening text	***CRC screening test ordered (self reported by patients)*** FOBT: Intervention: 33.9% Control: 19.8% Difference: 14.1 (2.8–25.3) Flexible sigmoidoscopy: Intervention: 17.1% Control: 8.5% Difference: 8.5 (0.0–17.1) Either Intervention: 47.2% Control: 26.4% Difference: 20.7 (8.6–32.9) ***CRC screening test ordered (according to chart review)*** FOBT: Intervention: 33.6% Control: 20.9% Difference: 12.6 (1.7–23.6) Flexible sigmoidoscopy: Intervention: 18.4% Control: 7.3% Difference: 11.1 (3.0–19.3) Either Intervention: 40.8% Control: 23.4% Difference: 17.4 (6.0–28.8) ***Unadjusted Relative Risk for having a test ordered*** 1.79 (95% CI 1.23-2.58) ***CRC screening test completed (according to chart review)***	II A decision aid consisting of an educational videotape combined with a stages-of-change– based educational brochure and chart marker increased patient intent to request colon cancer screening, the proportion of patients who have screening tests ordered, and the proportion of patients who completed screening tests. The absolute difference in the proportion of patients who completed screening was 14.2 % (36.8% of the intervention group and 22.6% of controls).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
						FOBT: <u>Intervention:</u> 28.5% <u>Control:</u> 20.2% <u>Difference:</u> 8.3 (-2.4–218.9) Flexible sigmoidoscopy: <u>Intervention:</u> 17.6% <u>Control:</u> 4.8% <u>Difference:</u> 12.8 (5.1–20.4) Either <u>Intervention:</u> 36.8% <u>Control:</u> 22.6% <u>Difference:</u> 14.2 (3.0–25.4) ***Mean score for intent to ask for screening (±)*** <u>Intervention:</u> 3.1 ± 1.0 <u>Control:</u> 2.5 ± 1.1 $p<0.001$	

Quality assessment: 15% of the potential participants were randomised (reasons fully described); adequate randomisation (random-number generator centrally performed, not balanced among centres); adequate allocation concealments (central randomisation, assignments placed in sealed, opaque, sequentially numbered envelopes); blinded assessment of participants' status examined in a standardized and validated manner.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Robb 2006 and Robb 2008	RCT	(1) control group: no information leaflet; (2) risk information group: leaflet on risk factors for colorectal cancer (key messages (3) risk and screening information group: leaflet on risk factors for CRC plus information on CRC screening.	N = 3,365 men and women aged between 45 and 66 years Setting: General Practices in south-west England UK	Not reported	Primary: absolute and comparative risk judgments; Secondary: interest in screening	**Total knowledge score** Control: 4.95 (2.56) Risk info group: 8.41 (2.28) Risk and screening info: 8.15 (2.60) $F_{(2, 1944)} = 388.63$, p=0.01 **STAI anxiety mean (SD)** Control: 10.66 (3.79) Risk info group: 10.58 (3.66) Risk and screening info: 10.78 (3.83) $F_{(2, 1931)} = 0.47$, P = 0.63 **Comparative perceived risk M (SD)** Control: −0.19 (0.67) Risk info group: −0.14 (0.71) Risk and screening info: −0.19 (0.72) $F_{(2, 1902)} = 1.16$, p = 0.314 **Absolute perceived risk M (SD)** Control: 33.4 (20.9) Risk info group: 34.7 (21.0) Risk and screening info: 34.4 (20.8) $F_{(2, 1804)} = 0.59$, p = 0.553 **Interest in screening (% interested)** Control: 93.5 Risk info group: 92.1 Risk and screening info: 92.6 $\chi^2(2, n = 1923) = 1.01$, p =0.603	**II** Significant comparative optimism and high numeric estimates of absolute risk were found. Risk factor information did not reduce optimistic beliefs nor modify estimates of risk. Interest in screening was high overall and not influenced by the information

Quality assessment: simple random allocation; GPs were blind to group allocation; 1945/3188 (61%) questionnaires were returned; intention to treat analysis.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Ruffin 2007	RCT	Intervention: Colorectal Web, is an **interactive program** that can be presented as a Web site or stand-alone programme focused on helping adults establish a preference among the various options for screening for CRC (objective presentation of the screening options, including FOBT, flexible sigmoidoscopy, colonoscopy, and double contrast barium enema). Direct comparison between all of the screening options.

Control: CRC Web site carefully selected by the investigators as reflecting the standard, state-of-the-art, non-interactive format. Very similar to the intervention programme with the exception of interactivity | 174 participants Aged 50-70 year old

Urban (Detroit), suburban (Flint, Saginaw), and rural (St. Joseph, Benton Harbor)

May 2002-December 2003 USA | 2, 8, 24 weeks | Primary: any type of CRC screening (yes/no) assessed by telephone interview

Secondary: preferred method for CRC screening | ***Participants having any type of CRC screening***
2 and 8 week follow up:
No significant difference between groups
24 week follow up:
Participants in the intervention group were significantly (p=0.035) more likely to get screened for CRC than the control arm.

Participants with a preferred type of screening
2 weeks follow up:
Participants in the experimental study arm were significantly (p<0.0001) more likely to have a preferred colorectal screening method compared to the control study arm, even after adjusting for baseline preference.
8 and 24 weeks follow up:
No significant difference between groups
The significant difference did not persist at 8 and 24 weeks follow up.

Number of screened participants according to type of screening
Overall
Control: 33
Intervention: 56
FOBT
Control: 49%
Intervention: 48%
Flexible sigmoidoscopy
Control: 15%
Intervention: 18%
Colonoscopy
Control: 36%
Intervention: 34%
No statistically significant difference between the study arms on type of CRC screening completed. | **II**

Exposure to the interactive decision aid Colorectal Web significantly increased the percent of adults screened for CRC compared to the control exposure |

Quality assessment: adequate randomisation and concealment (a block randomisation process programmed by the study computer support staff and verified by a statistician was used including two strata, race and gender); blinding to study arm assignment of investigators, data collectors, data entry, and data analysis. The study participants were blind to study arms since they were not aware of content difference between the two sites. 174/229 eligible participants were randomised (reasons fully reported).

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Stokamer 2005	RCT	Recommended screening: FOBT Intervention: 2-page intensive patient information handout with specific information on dietary and medication restriction, how to collect the samples, and how to complete the test. The patients also received a one-on-one 10- to 15-minute educational session on the importance of CRC screening and FOBT by a trained nurse (how the FOBT kit works, what a positive or negative result means, what would happen if the test was positive-colonoscopy-as well as what would happen if the test was negative-annual FOBT and flexible sigmoidoscopy every 5 years). Control: standard patient education (FOBT cards and an enlarged version of the manufacturer's instructions explaining how to properly collect stool specimens, prepare the cards for FOBT, and return them to the clinic).	788 patients, 50 years of age and older setting: primary care clinics August 1 and November USA	6 months	Primary: proportion of patients who returned the FOBT cards within 6 months	***Proportion of patients who returned the FOBT cards*** Overall: 462/788 (58.6%; 95% CI 55.1% to 62.1%) Control: 51.3%; Intervention: 65.9% p<0.001	**II** The proportion of patients who returned the FOBT cards was significantly higher in the intensive education group than with those who received standard education. Although the intervention was effective in improving FOBT return rates, one-on-one patient education by registered nurses is costly and time consuming (data not showed)

Quality assessment: adequate randomisation (using sequentially numbered, sealed, opaque envelopes which were given to the primary care nurses); intention to treat analysis; 788/794 (99.2%) participants were randomised; no information on contamination bias protection.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Tilley 1999	RCT	Recommended screening: digital examination, FOBT, flexible sigmoidoscopy Intervention (N=15, participants: 2261) Company-sponsored screening programme plus an enhanced health promotion programme (nutrition and ColoRecord intervention) Control (N=13, participants: 2827) standard care (Company-sponsored screening programme)	28 worksites more than 5000 participants Setting: February 1993-January 1995 USA	2 years	Primary: compliance with screening (one or more screening examinations in both the first and second years) Secondary: coverage (participant ask to attend at least one screening examination)	*Compliance with screening* Intervention: 36%±4 Control: 35±1 OR: 1.46 (95% CI 1.1-2.0); p=0.006 *Coverage* Intervention: 61%±3 Control: 61±1 OR: 1.33 (95% CI 1.1-1.6); p=0.002 *Compliance confirmed by worksite documentation* Intervention: 23%±3 Control: 19±1 OR: 1.71 (95% CI 1.1-2.7); p=0.012 *Coverage confirmed by worksite documentation* Intervention: 47%±4 Control: 44±2 OR: 1.57 (95% CI 1.2-2.0); p<0.001	**II** Adding a personal tailored behavioural intervention to a standard CRC screening programme can promote continued employee participation in screening as measured by compliance

Quality assessment: unit of randomisation: worksite; randomisation stratified on worksite location; unclear method of randomisation and allocation concealment; intention to treat analysis; 4963/5042 participants were included in the analysis.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Wardle 2003	RCT	Recommended screening: Flexible sigmoidoscopy Intervention: mailed psycho-educational intervention (booklet) around 2-3 weeks before screening invitation Control: usual screening invitation	2,966 patients enrolled within the FS Trial population aged 55-64 years Setting: primary care UK	Not reported	Screening attendance rate Cognitive and emotional effects (assessed through a questionnaire) Behaviour Screening attitudes and expectations	**Attendance rate** Control: 19.9% Intervention: 53.5% p<0.05 **Questionnaire response rate** 53.7% No difference between groups **Negative screening attitude (%, SD)** Control: 17.4, 3.9 Intervention: 16.5, 3.8 p<0.001 **Positive screening attitude (%, SD)** Control: 27.8, 3.2 Intervention: 28.7, 2.9 p<0.001 **Estimate of % who would go for test (%, SD)** Control: 47, 19.1 Intervention: 52.6, 18.6 p<0.001 **Screening intention (%,)** Control: very likely 29; likely 58; unlikely 10; very unlikely 4. Intervention: very likely 43; likely 50; unlikely 5; very unlikely 2. p<0.001	**II** In this RCT a 3.6% increase in the screening attendance rate was observed after a mailed psycho-educational intervention aimed at address perceived barriers to the test.

Quality assessment: unclear randomisation and allocation concealment; no information on type of analysis, and on protection against contamination.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Wolf 2000	RCT	Recommended screening: faecal occult blood test (FOBT) and flexible sigmoidoscopy Relative risk reduction (RRR) information script: 3-minute discussion of FOBT, flexible sigmoidoscopy and the evidence supporting mortality reduction in general population described in terms of relative risk reduction Absolute risk reduction (ARR) information script: identical to the RRR information script, except that CRC mortality reduction was described in terms of absolute risk reduction Control script: brief description of FOBT and flexible sigmoidoscopy	399 patients ≥65 years Primary care (one university-based, one suburban, one rural office practice, and one rural community health center) July 1996-November 1997 USA	Not reported	Primary: interest in beginning or continuing CRC screening (FOBT and flexible sigmoidoscopy) measured on a 5-point Likert scale and intent to begin or continue CRC screening as dichotomous (yes/no) variable Secondary: patients estimate of FOBT positive predictive value and patients' perceptions of CRC mortality reduction	***Interest and intent to undergo CRC screening among elderly patients*** ***Interest in undergoing screening*** Probably or definitely interested in FOBT Control: 51.9% RRR Info Group: 54.4% ARR Info Group: 51.5% p value: 0.9 Probably or definitely interested in flex sig Control: 32.2% RRR Info Group: 36.0% ARR Info Group: 32.3% p value: 0.8 ***Intent to undergo screening*** Intent to begin or continue FOBT Control: 55.6% RRR Info Group: 61.0% ARR Info Group: 55.4% p value: 0.6 Intent to begin or continue flex sig Control: 32.3% RRR Info Group: 36.0% ARR Info Group: 32.3% p value: 0.8 Intent to begin or continue FOBT and/or flex sig Control: 59.4% RRR Info Group: 66.9% ARR Info Group: 63.1% p value: 0.4	II No significant difference in screening interest or intent to begin or continue CRC screening among the three groups. Information about CRC screening and its potential effect on mortality whether couched in terms of relative or absolute risk reduction, had no impact on screening interest or intent among elderly primary care patients.

Quality assessment: unclear randomisation and allocation concealment; 399/868 (58%) of the screened population were randomised.

Author, publication year	Study design	Intervention	Participants	Follow up	Outcome	Results	Level of evidence Conclusions
Zapka 2004	RCT	Recommended screening: sigmoidoscopy Intervention: a home-mailed video intended to encourage discussion of CRC screening with the primary care provider and increase use of screening, particularly by sigmoidoscopy. The video, hosted by a nationally known actress who has had colorectal cancer, addressed benefits and barriers to sigmoidoscopy, primarily with clips of several patients who had screening detected CRC, and featured patients discussing sigmoidoscopy experiences Control: usual care	938 patients age 50 to 74 years who were scheduled for an upcoming physical examination setting: community practice, 5 primary care practices in central Massachusetts (USA) February 1999 through December 2000	4-6 months	Primary: receipt of sigmoidoscopy (with or without any other test) with receipt of all other tests (and combination of tests) and with receipt of no tests assessed through telephone surveys Secondary: Number of screening test according to the viewing in intervention group	***Sigmoidoscopy with or without any other test n (%)*** Control: 104 (21.3) Intervention: 118 (26.2) Odds ratio: 1.22 (95% CI 0-88-1.70) ***Other test combination n (%)*** Control: 166 (34.0) Intervention: 130 (28.9) Odds ratio: 0.84 (95% CI 0.63–1.14) Number of screening test according to the viewing in intervention group ***Sigmoidoscopy with or without any other test n (%)*** Control: 104 (21.3) Intervention (viewing <50% of video): 43 (16.7) Odds ratio: 0.62 (95% CI 0.41-0.93) Intervention (viewing 50-100% of video): 75 (38.9) Odds ratio: 2.81 (95% CI 1.85-4.26) ***Other test combination n (%)*** Control: 166 (34.0) Intervention (viewing <50% of video): 68 (26.5) Odds ratio: 0.61 (95% CI 0.43-0.87) Intervention (viewing 50-100% of video): 62 (32.1) Odds ratio: 1.45 (95% CI 0.96-2.20)	II In this trial a mailed video outreach strategy had no effect on the overall rate of colorectal cancer screening and did not increase screening with sigmoidoscopy.

Quality assessment: adequate randomisation (computer-generated sequence) and allocation concealment (centralised computer-generated assignment); 1788 participants contacted by phone 1575 (88%) consent to participate. Interviewers were blinded. People who reported that they were scheduled for procedure (n=39) and lost to follow up (n=20) were classified as not screened.

10.2 Additional evidence tables prepared after December 2009

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Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Braun K.L., 2005	To test an intervention based on social learning theory (SLT) to improve colorectal cancer (CRC) screening among Native Hawaiians, a group with low CRC screening rates. Randomised controlled trial USA	121 members from Sixteen Hawaiian civic clubs aged 50 and older. Eight civic clubs were randomised to control group (control group: n=52; mean age 65.77; 75% female) and eight clubs to intervention group (experimental group: n=69; mean age 65.68; 70% female). No significant difference between groups on any of the demographic variables. Participants completed a demographic survey and a pre and post intervention test of knowledge, attitudes, and behaviors related to CRC screening.	Culturally targeted presentation and a free Faecal Occult Blood Test (FOBT) Control group: delivered by a non hawaiin nurse and a single reminder call (n=52) or Intervention group: in line with SLT, education was delivered by a Native Hawaiian physician and Native Hawaiian CRC survivor, and members received an FOBT demo, were challenged to involve a family member in screening, and were telephoned multiple times to address change-related emotions and barriers (n=69).	Compliance, Knowledge score (0-10); attitudes 8range4-40);intention (range 3-12), self-efficacy (range 3-12)	**CRC screening behaviours post intervention, n (%)** Completed free FOBT Intervention=23 (33) Control group =21 (40) First time screener Intervention=5 (22) Control group =8 (38) Took FOBT kit for family member Intervention=20 (29) Control group =N/A Screened, either through intervention and/or on own Intervention=46 (67) Control group =44 (85) unscreened Intervention=23 (33) Control group =8 (15) $p<0.05$ **Knowledge CRC screening** Intervention (pre vs post)=5.14 vs 8.12 $p<0.001$ Control (pre vs post)=5.11 vs 8.57 $p<0.001$ **Attitudes** Intervention (pre vs post)=28.97 vs 34.47 $p<0.001$ Control (pre vs post)=29.08 vs 33.13 $p<0.001$ **Intention** Intervention (pre vs post)=8.61 vs 10.71 $p<0.001$ Control (pre vs post)=9.38 vs 11.02 $p<0.001$ **Self-efficacy** Intervention (pre vs post)=8.73 vs 11.17 $p<0.001$ Control (pre vs post)=9.74 vs 11.54 $p<0.001$	**II** For Native Hawaiian individuals belonging to a network of civic clubs, an intervention based on SLT delivered by a Native Hawaiian physician and CRC survivor was less effective at further increasing compliance than was a culturally targeted educational session delivered by a non-Hawaiian nurse. That CRC screening compliance was high prior to our intervention suggests that we targeted a very health conscious segment of the Native Hawaiian population. Future work should focus on underserved segments of this indigenous group.

Quality assessment: allocation concealment: coin toss; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; four participants lost at follow up; post test data collected for 121 members (so analyses were limited to the 121).

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Campbell M.K., 2004	To measure the relative effectiveness of two different theory-based strategies: individualized tailored print newsletters and targeted videotapes (TPV) and a lay health advisor (LHA) intervention. Randomised controlled trial (WATCH project) USA	587 (mean age 52 years) African American active members of 12 rural North Carolina churches were randomised were randomised to LHA group, TPV group, combined and control group. Baseline and telephone interviews. No significant difference between groups on any of the demographic variables.	Strategies to promote colorectal cancer preventive behaviors: LHA only = a lay health advisor intervention (n=51). TPV only = a tailored print and video intervention, consisting of 4 individually tailored newsletters and targeted videotapes (n=123) Combined = LHA in combination with TPV (n=176) Control =health education session and speaker on topics not directly related to the study (n=129)	Compliance with FOBT and other CRC screening	Analyses of the intervention effect on screening was limited to participants age 50 and over (n=287) **N** Contol=69 LHA only= 51 TPV only=76 Combined=87 **FOBT test in the past year, %** <u>Baseline</u> Contol=30.4 LHA only= 23.5 TPV only=19.7 Combined=19.5 p=0.36 <u>Follow-up</u> Contol= 21.7 LHA only= 33.3 TPV only= 36.8 Combined= 31.0 p=0.08 **Other CRC test in the past yar, %** <u>Baseline</u> Contol=20.3 LHA only= 19.6 TPV only=23.7 Combined=26.4 p=0.75 <u>Follow-up</u> Contol= 27.5 LHA only= 25.5 TPV only= 21.1 Combined= 14.9 p=ns	**II** The TPV intervention, consisting of four computer-tailored newsletters and four targeted videotapes demonstrated the most improvement in FOBT compliance (87% increase over baseline levels), although the result had marginal significance statistically. The TPV-only group achieved the amount of increase in proportion to those screened by FOBT (15%) that was hypothesized in the original study design and power calculations. The study findings failed to confirm the hypothesis that a multicomponent approach combining a tailored and a targeted home-based intervention with a lay helping, church-based intervention would be more effective than either intervention alone. Indeed, the study did not demonstrate efficacy of the LHA intervention either alone or in combination with TPV.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: no; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Chan E.C.Y., 2008	To develop and implement an electronic intervention, the InterNet LETter (NetLET), to increase interest in and use of CRCS among patients with and without e-mail access at home or work. Randomised controlled trial USA	97 patients over 49 years old were recruited during a clinic appointment between 2004 and 2005. Patients with e-mail at home or work were assigned to the private access arm (n=77; mean age 58.8 years; 54.6% female); patients without e-mail but willing to use the public library system were assigned to the public access arm (n=20mean age 65.8 years; 75% female).Within each arm, patients were randomised to the NetLET or control group. Participants completed a self-administered survey at the beginning and a follow-up survey 2 months after enrolment for controls and 2 months after final intervention for intervention group.	Intervention to promote colon cancer screening through e-mail over the internet: Intervention group: participants were e-mailed the NetLET, a personalized e-mail from the physician reminding the patient to undergo CRCS and providing a link to a webpage with information about CRCS (n=42 in the private access arm; n=11 in the public access arm). Control group: controls were mailed a reminder letter from their physician and a FOBT kit (n=35 in the private access arm; n=9 in the public access arm).	CRCS intention; completion of FOBT; computer, internet and e-mail use, information seeking	**Plan to make appointment with doctor for screening in next 6 months, n (%)** Strongly agree Private access=18 (23.4) Public access =5 (25.0) Agree Private access=27 (35.1) Public access =6 30.0) **Completion of FOBT, n (%)** Private access Intervention= 11/42 (26) Control= 8/35 (23) Public access Intervention= 0/11 Control= 3/9 (33) **Follow up survey of the private access arm, n(%)** Intervention = 28 Control= 24 Received e-mail reminder to get screened Intervention= 12 (42.9) Control= 1 (4.2) During study, communicated with doctor by e-mail Intervention= 11 (39.3) Control= 0 (0.0) If yes, Will continue using MyCareLINK Intervention= 7 (63.6) Control= N/A Discussed CRCS: No one Intervention= 2 (6.9) Control= 5 (16.7)	**II** It was not feasible to implement the NetLET intervention, but the reasons differed for the private and public access arms. In the private access arm, the authors were unable to overcome system barriers while in the public access arm, the authors were unable to recruit participants and to overcome barriers to accessing and using e-mail. These differences suggest that health promotion interventions that attempt to bridge the digital divide will need, at a minimum, to ensure convenient access to the internet and to equip participants with the skills needed to use a computer and the internet. The potential to develop an electronic highway between clinics and homes, health care providers and patients, is enormous and can create opportunities for patients to engage in informed decision making and for patients and physicians to engage in shared decision making.

| | | | | Discussed CRCS: Doctor
Intervention= 24 (82.8)
Control= 18 (60.0)

Discussed CRCS: other
Intervention= 3 (10.3)
Control= 7 (23.3) | |

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; follow up survey: response rates in the private access intervention and control groups were 69% (29/42) and 86% (30/35). For the public access arm, they were 9% (1/11) and 67% (6/9) for the intervention and control groups.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Christie J., 2008	To determine whether a patient navigator will enhance CRC screening by colonoscopy beyond physician recommendation alone. Prospective randomised controlled trial USA	21 patients (mean age 58 years; 755 female), who were asymptomatic for gastrointestinal symptoms, were in need of screening, had a primary care physician and had received a referral for screening colonoscopy. After the referral patients were randomly assigned to either receive navigation (PN+ group) to screening colonoscopy or not receive navigation (PN- group).	Colonoscopy screening: PN+ group: the patient navigator reviewed the referral form, added any necessary information and faxed it to the GI scheduler. (n=13). PN- group: the physician completed the referral form, placed it in the medical chart, and the medical assistant faxed it to the GI scheduler. (n=8).	Completion rate, patient satisfaction	**Completion rate, %** Navigated =53.8 Nonnavigated= 13 (p=0.085) **Refuted screening colonoscopy, %** Navigated =23 Nonnavigated= 63 No difference in preparation quality (p=0.10) **Patient satisfaction** 100% of navigated patients were very satisfied with navigation services. 70% of the navigated patients reported that they would refer family and friends for a colonoscopy.	**II** Results showed promising results in this small randomised trial of the effectiveness of a patient navigator in increasing screening colonoscopy rates in low-income minorities. It is of particular importance to gain a better understanding of certain screening behaviors in this group, as they are disproportionately burdened with cancer. Further study into the factors that impact success and cost effectiveness of patient navigators is required.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Dietrich A.J., 2006	To evaluate the effect of a telephone support intervention to increase rates of breast, cervical, and colorectal cancer screening among minority and low-income women. Randomised controlled trial USA	1,413 women aged 50 to 69 years of age from 11 community and migrant health centers in New York City who were overdue for at least cancer screening. Women were randomised to receive an average of 4 calls from prevention care managers (intervention group= 696; mean age 58.1±5.3) or usual care (control group= 694; mean age 58.1±5.2).	Control group: the usual care group received a single telephone call during which trial staff answered questions about preventive care, informed women of their usual care status, advised them to obtain needed preventive care from their primary care clinician, and thanked them for their participation (n=707). Intervention group: the intervention group received a series of telephone support calls from a trained prevention care manager who guide women through the health care system during cancer treatment, prevention care managers facilitated the screening process for each woman by addressing barriers that prevent or delay receipt of cancer screenings (n=706).	Proportion of women up to date for cancer screening	**Proportion of women up to date for cancer screening, percentage points** Mammography *Change from baseline (CI)* Intervention group = 0.10 (0.05 to 0.15) Control group = -0.02 (-0.08 to 0.02) Difference (95%CI)=0.12 (0.06 to 0.19) Papanicolaou test *Change from baseline (CI)* Intervention group = 0.07 (0.03 to 0.11) Control group = 0.00 (-0.03 to 0.05) Difference (95%CI)=0.07 (0.01 to 0.12) Any colorectal screening *Change from baseline (CI)* Intervention group = 0.24 (0.20 to 0.29) Control group = 0.11 (0.08 to 0.16) Difference (95%CI)=0.13 (0.07 to 0.19) Up to date for 3 screenings *Change from baseline (CI)* Intervention group = 0.22 (0.18 to 0.27) Control group = 0.08 (0.04 to 0.12) Difference (95%CI)=0.14 (0.08 to 0.20)	**II** Telephone support can improve cancer screening rates among women who visit community and migrant health centers. The intervention seems to be well suited to health plans, large medical groups, and other organisations that seek to increase cancer screening rates and to address disparities in care.

Quality assessment: allocation concealment: adequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; 10 women from intervention group and 13 women from control group were excluded because medical records were unavailable.

Author, publication year	Study Objective Study Design	intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
Fox R., 2006	To review studies of the effectiveness of leaflets in promoting informed choice in screening. Systematic rewiew of of randomised controlled trials (RCTs) that had attempted to determine the contribution of leaflets to the exercise of informed choice in screening decisions	Leaflets to promote informed choice in screening	9 RCT contained sufficient information about the intervention to allow assessment of the information provided. 5 studies about prostate cancer screening; 2 studies about Down's syndrome screening, 1 studies about genetic screening and 1 about pancreatic cancer screening	Knowledge, attitudes to screening, intention to be screened, uptake, anxiety, satisfaction with decision-making, discussions about screening with care providers and agreement that enough information had been provided to allow informed choice.	**Knowledge** 7 studies with this outcome: 5 showed significantly increased knowledge in the intervention group compared with controls. The evidence that written information promotes informed choice is unconvincing: in one study, >40% men in all groups felt that the information was advocating screening. **Decision making** 6 studies with this analysis: 4 found no difference between intervention and control groups, in 1 the intervention group was more likely to discuss screening with their doctor, and in 1 the intervention group was more likely to feel they could make an informed choice. **Screening uptake** 5 studies compared intention to be screened: in 1, the intervention group displayed less desire for screening than the controls; none of the 4 studies with screening uptake as an outcome measure found any effect of the intervention.	**I** Research into informed choice in screening is hampered by the lack of agreement about its definition and measurement. The most effective way for screening programmes to achieve informed choice is unclear. Programmes should not rely solely on providing written information but should explore additional ways to promote informed choice.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE: EMBASE: CINAHL: BRITISH NURSING INDEX, COCHRANE LIBRARY, NHS, CRD, NICE, JOURNAL OF MEDICAL SCREENING
	Date restriction	up to 2006.
	any restriction	only English published studies done in North America
Selection	Inclusion and exclusion criteria	randomised controlled trials (RCTs) that had attempted to determine the contribution of leaflets to the exercise of informed choice in screening decisions
Validity assessment	Criteria and process used	Performed using validated checklist
Data abstraction	Process used	Performed by two authors independently
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	yes
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	yes
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results presented narratively

Author, publication year	Condition	Study Objective Study Design	Participants	Outcome	Results	Conclusion Level of evidence
Geller B.M., 2008	PPCA intervention vs no intervention	To test a computer-based intervention, the Patient / Provider Communication Assistant (PPCA), to facilitate discussion and provider recommendations for CRC screening. Pre-post quasi-experimental design (pilot study)	319 patients (aged 50-80 years)from 5 practices in rural communities. The control group (n=177; 42.4% male) during 1 week was invited by their primary care provider to participate in a 5 minute exit interview concerning discussion and recommendations from providers, and patient intentions regarding colorectal screening. The intervention group (n=142; 41.2%) was recruited in an equivalent way about 1 month later to participate in the PPCA intervention immediately before their visit. Patients answered questions on the PPCA about their history of CRC screening, intentions to screen in the future and risk factor information.	Patients' intentions to obtain CRC screening, provider discussion and recommendation	**Dr talked about CRC screening, n(%) *p*** Comparison: 50 (29.6) Intervention: 71 (54.2) p=0.04 **Dr talked about colonoscopy, n(%) *p*** Comparison: 43 (25.3) Intervention: 67 (51.2) p=0.04 No significant difference about sigmoidoscopy and FOBT. **Dr recommended CRC screening, n(%) *p*** Comparison: 38 (23.0) Intervention: 64 (49.2) p=0.02 **Dr recommended colonoscopy, n(%) *p*** Comparison: 30 (18.1) Intervention: 56 (43.4) p=0.01 No significant difference about sigmoidoscopy and FOBT. **Participants not currently up to date on CRC screening plan to get screened, n(%) *p*** Comparison: 23 (43.4) Intervention: 45 (91.8) p=0.01 No significant difference about to get a sigmoidoscopy, to do a FOBT, to get a colonoscopy. **All participants plan to get screened, n(%) *p*** Comparison: 88 (50.6) Intervention: 121 (91.7) p=0.003 **All participants plan to get a colonoscopy, n(%) *p*** Comparison: 58 (33.1) Intervention: 94 (72.3) p=0.003 No significant difference about to get a sigmoidoscopy, to do a FOBT. Ninety-five percent of the patients regardless of age or education found the PPCA easy to use.	**III** Results indicated increased provider discussion and recommendation, and patients' intentions to obtain CRC screening, and in particular colonoscopy, for patients exposed to the intervention, regardless of the patients' age or literacy levels. The PPCA is a promising intervention method that is acceptable to rural patients

Quality assessment: patients not randomly allocated.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcome	Results	Level of evidence Conclusions
Hudson S.V., 2007	To determine if the inclusion of office staff in general behavioral counseling activities has the added benefit of enhancing rates of colorectal cancer screening. Cross-sectional survey U.S.A	Random sample of patients from 22 New Jersey and Pennsylvania family medicine practices eligible for CRC screening (aged 50-70 years). N=795; 55% men; mean age 59.30±5.84 Medical record review; practice managers and lead physicians completed a 46-item practice information survey on topics such as patient population, staff turnover, use of clinical reminder and prevention systems, and implementation of electronic medical records.	Practices with or without nursing or health educator staff to provide behavioral counseling to patients on topics such as diet, exercise or tobacco use	CRC screening correlates: practice use of reminder system, non physical staff for behavioural counselling, health risk assessments, counselling.	**Number screened (%)** Male= 151 (34.7) Female= 98(27.2) Tot= 249 (31.3) Multivariate analysis on CRC screening: **Practice use of reminder system, z-score, p value OR (95%CI)** With vs Without: z=4.96, p<0.0001 OR= 2.57 (1.77-3.74) **Non-physician staff for behavioural counselling** With vs Without: z=7.30, p<0.0001 OR= 2.96 (2.21-3.96) **Health risk assessments** With vs Without: z=-0.44, p=0.6625 OR= 0.92 (0.64-1.33) Multivariate analysis separately for each category of counselling on CRC screening: **Practice use of counselling for, z-score, p value OR (95%CI)** **physical activity** With vs Without: z=3.77, p=0.0002 OR= 2.40 (1.52-3.80) **Eating** With vs Without: z=1.78, p=0.1383 OR= 1.51 (0.88-2.59) **Tobacco** With vs Without: z=3.02, p=0.0025 OR= 2.19 (1.32-3.66)	**V** These findings suggest that interventions to achieve better CRC screening rates do not need to focus solely on CRC. Higher CRC rates may be achieved by capitalizing on the enhancing contributions of nonphysician practice members providing more general health behavior change patient education.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Jandorf L., 2005	To determine whether a PN would enhance CRC screening participation beyond physician recommendation alone in a neighborhood health care setting. Prospective randomised controlled trial USA	78 patients aged 50 or older attending a primary care practice who had not had a faecal occult blood test within the past year, a sigmoidoscopy or barium enema within the past 3-5 years, or a colonoscopy within the past 10 years were randomly assigned either to receive navigator services (PN+ group; n=38; mean age 61.1±7.2; 76.3% female) or not to receive navigator services (PN-group; n= 40; mean age 61.3±8.4; 72.5% female). No demographic differences between the two groups.	CRC screening: <u>PN+ group</u>: participants were assigned to the PN for assistance with completing the screening process, including the FOBT cards and endoscopic procedures that had been recommended by their physician. The PN provided written reminders, telephone calls, and/or scheduling assistance to the participants, encouraging participation in CRC screening (n=38). <u>PN- group</u>: usual care; participants were asked by their physician to complete FOBT cards and were recommended to undergo endoscopic screening (either FS or colonoscopy) (n=40).	Compliance with screening	**Completed FOBT after 3 weeks (before navigation), % yes** PN+ =26.3 PN-= 17.5 (p=ns) **Completed FOBT after 3 months , % yes** PN+ =42.1 PN-= 25.0 (p=0.086 ns) **Had endoscopy appointment at 3 months , %** PN+ =18.4 PN-= 0 (p=0.005) **Completed endoscopy at 3 months, %** PN+ =15.8 PN-= 5.0 (p=0.115 ns) **Completed endoscopy at 6 months, %** PN+ =23.7 PN-= 5.0 (p=0.019)	**II** Results demonstrate that within 6 months after physician recommendation for CRC screening, a PN system was effective at ensuring that significantly more patients received CRC screening by endoscopy. In addition, the PN·group showed a trend toward increased completion of FOBT cards after 3 months, although this trend did not reach statistical significance. These findings therefore suggest that in a predominantly poor, urban, minority population, PNs can have a positive impact on CRC screening, with the potential for reducing the mortality from CRC.

Quality assessment: allocation concealment: unclear; blindness of provider: yes; blindness of patients: no; blindness of outcome assessor: yes; 6 lost at follow up.

Author, publication year	Study Objective Study Design	intervention	Included studies	Outcomes	Results	Conclusion Level of evidence
Jimbo M., 2006	To examine the literature on information technology impact on the delivery of cancer preventive services in primary care offices. Systematic review on information technology impacts on cancer prevention.	Patient and/or provider computer reminder	30 studies on primary breast cancer, cervical and colorectal cancer, the majority were RCTs, the other were interrupted time series analysis. 14 studies were limited to just providers. In 13 studies, the intervention is limited to during the time of the appointment. Half of the studies were conducted in academic or training sites. All of the studies have used opportunistic screening; none limited the intervention to periodic or health maintenance appointments. The duration of theinterventions were 6 months to 5 years, with the most common being 1 year.	Effectiveness of information technology on cancer screening	Technology interventions studied to date have been limited to some type of reminder to either patients or providers. Patient reminders have been mailed before appointments, mailed unrelated to an appointment, mailed after a missed appointment, or given at the time of an appointment. Telephone call interventions have not used technology to automate the calls. Provider interventions have been primarily computer-generated reminders at the time of an appointment. However, there has been limited use of computer-generated audits, feedback, or report cards. The effectiveness of information technology on increasing cancer screening was modest at best. 13 studies evaluating the effect on ICT(information and communication technologies) generated reminders in FOBT CRC screening: 8 out of 13 studies showed that reminders increased FOBT screening participation.	I The effectiveness of the information technology on increasing cancer screening was modest at best. There are some limitations in making the comparison across study designs that range from pre- and postdesigns to randomised control trials. There is critical need to study these new technologic approaches to understand the impact and acceptance by providers and patients.

Quality of reporting (QUOROM CHECKLIST)

METHODS SEARCH	DATABASES, REGISTER, HAND SEARCHING;	MEDLINE: EMBASE: CINAHL: CCRCT: SCIENCE CITATION INDEX:
	Date restriction	up to 2005.
	any restriction	only English published studies done in North America
Selection	Inclusion and exclusion criteria	Inclusion criteria not stated. Exclusion criteria: review, opinion article, descriptive of a new technology, or was used in a health context not readily available in the United States
Validity assessment	Criteria and process used	Not reported
Data abstraction	Process used	Not reported
Quantitative data synthesis	Measures of effect, method of combining results	Meta-analysis not performed
Results Trial flows	Trial flow and reason for exclusion	Not reported
Study characteristics	Type of studies, participants, interventions, outcomes	yes
Study results	Descriptive data for each trial	yes
Methodological quality	Summary description of results	Not reported
Quantitative data synthesis	Agreement on the selection and validity assessment;	Non reported
	summary results	Results presented narratively

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Lairson D.R., 2008	To determine the cost-effectiveness of targeted and tailored behavioral interventions to increase CRC screening use by conducting an economic analysis associated with a randomised trial among patients in a large, racially and ethnically diverse, urban family practice in Philadelphia. Randomised controlled trial (cost effectiveness analysis) USA	1,546 patients aged 50 to 74 years (66.8% female) from a large urban family practice in Philadelphia with no prior diagnosis of colorectal neoplasia were randomised to receive usual care (control group: n=387), a mailed standard intervention (standard intervention group: n=387), a standard intervention plus 2 tailored message pages (tailored intervention group: n=386) and a tailored intervention plus a telephone call (TIP group: n=386) No significant difference among groups on any of the demographic variables. Participants in each of the intervention groups (SI, TI, and TIP) received 2 "rounds" of contact. Participants completed a baseline, midpoint and endpoint survey.	Control group (C): usual care(n=387; 66.1% female) or Standard intervention group (SI): received a mailed standard intervention (ie, a CRC screening invitation letter, SBT cards, informational booklet, and reminder letter). (n=387; 66.7% female) Tailored intervention group (TI): participants were sent the standard intervention plus 2 tailored "message pages." These pages included brief messages that addressed barriers to SBT and FS screening (n=386; 67.9% female) Tailored intervention plus telephone call group (TIP): received the tailored intervention plus a telephone call were mailed the standard intervention and the tailored message pages and also were designated to receive 1 reminder telephone call for each round of the intervention. (n=386; 66.6% female)	Cost-effectiveness analysis; sensitivity analysis	**Total direct cost, $** SI=12515 TI=44522 TIP=59500 **Overhead (30%of direct cost), $** SI=3755 TI=13357 TIP=17850 **Total cost, $** SI=16270 TI=57879 TIP=77350 **Cost per individual, $** SI=16270 TI=57879 TIP=77350 **Cost per additional individual screened, $** C=0 SI=42.04 TI=149.94 TIP=200.39 **Incremental cost-effectiveness, $** C=- SI=319 TI=Dominated TIP=5843 **Sensitivity analysis** ICER (effect size 95%CI; overhead=from 25% to 35% of direct cost): SI vs usual care ranged between $300 and $339 TIP vs SI ranged between $5550 and $6113	**II** The targeted intervention was more effective and less costly than the tailored intervention. Although tailoring plus reminder telephone call was the most effective strategy, it was very costly per additional individual screened. Mailed SBT cards significantly boosted CRC screening use. However, going beyond the targeted intervention to include tailoring or tailoring plus reminder calls in the manner used in this study did not appear to be an economically attractive strategy.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Lewis C.L., 2008	To determine whether a multi-modal intervention, which included mailing a patient reminder with a colon cancer screening decision aid to patients and system changes allowing direct access to screening test scheduling, would be an effective and efficient means of promoting colon cancer screening in primary care practice. Pilot quasi controlled trial USA	237 patients (aged 50 to 75 without colon cancer screening) of attending physician in an academic practice in North Carolina. 137 listed alphabetically were assigned to intervention group (mean age 62 years; 60% female) 100 patients were assigned to control group (mean age 62 years; 61% female) No differences between the two groups in regards to age, sex and race.	<u>Intervention group</u>: mailed package that included a reminder letter from their primary care physician, a colon cancer screening decision aid, an educational videotape, surveys to be completed before and after the video watching and instructions for obtaining each screening test without an office visit so that patients could access screening tests directly. <u>Control group</u>: no intervention	Screening test completion	**Response to mailing** Returned to sender: 9(6%) Did not return materials: 71(52%) Sent material back: 57 (42%) **Screening test completion, n(%)** I vs C: 20/137 (15%) *vs* 4/100 (4%) Difference: 11%; 95%CI:3-18 p=0.01	**II** A multi-modal intervention, which included mailing a patient reminder with a colon cancer decision aid to patients and system changes allowing patients direct access to schedule screening tests, increased colon cancer screening test completion in a subset of patients within a single academic practice. Although the uptake of the decision aid was low, the cost was also modest, suggesting that this method could be a viable approach to colon cancer screening.

Quality assessment: allocation concealment: alphabetical; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes, none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Menon U., 2008	To test the efficacy of a computer-based intervention designed to increase CRC screening test use—that is, faecal occult blood test (FOBT), flexible sigmoidoscopy, or colonoscopy. Randomised controlled trial USA	199 patients from the Chicago metropolitan area (mean age 57.36±6.8; 71%male) were randomised to intervention (n=101) or control group (n=98). No significant difference in demographic characteristics by study groups.	Education on CRC screening: Intervention group: computer-based, theory-guided educational program called TIMS(Tailored Messaging Intervention System). In TIMS, participants answered a series of questions on the computer, using a touch-screen response format (n=101; 56.1%female). Based on their responses, participants received tailored messages on knowledge of CRC and screening, perceived barriers to each CRC screening test, benefits of each CRC screening test, perceived risk of CRC and self-efficacy regarding each CRC screening test. Control group : usual care (n=98; 43.9% female)	Perception of TIMS (Tailored messaging Intervention System); knowledge of CRC and screening; perceived risk, self efficacy preintervention.	**Participants' perception of TIMS (n=75 postintervention respondents)** Education helped to get CRC screening, n (%yes)=60 (80) Education was useful, n (%yes)=68 (90.7) Education raised new concerns, n (%yes)=51 (68.0) Education made you feel worried about CRC screening, n (%yes)=23 (30.7) Did anything about the education stand out, n (%yes)=35 (46.7) Would you change anything about the education, n (%yes)=9 (12.5) Would you tell others to use educational program if available, n (%yes)=72 (98.6) **Knowledge of CRC & screening (0-4), mean (SD)** I vs C= 0.64 (0.84) vs 0.91 (0.82) **Perceived risk of CRC (0-15), mean (SD)** I vs C= 3.6 (4.0) vs 3.9 (3.9) **FOBT self-efficacy (0-35), mean (SD)** I vs C= 21.6 (8.5) vs 25.8 (6.8) **Endoscopy self-efficacy (0-15), mean (SD)** I vs C= 41.3 (14.1) vs 47.7(11.6)	**II** The response rate of 83% demonstrated feasibility of conducting colorectal cancer education in the primary care setting. Participants' perceptions of TIMS were favourable as 90% of the sample indicated they found the information useful. Data showed that in this predominantly African American sample, there were no differences between participants in the intervention or control groups in knowledge or beliefs. Participants sought no help from attending data collectors and navigated the revised touch screen program with ease. Computer-based education is feasible in primary care clinics.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Nash D., 2006	To assess the impact of a hospital-based intervention aimed at eliminating health care system barriers to timely colorectal cancer screening at Lincoln Medical Center, a large, urban public hospital in one of the nation's poorest census tracts. Retrospective cohort USA	Patients who underwent screening and diagnostic colonoscopy at Lincoln Medical Center, a large, urban public hospital during 11-month period. N=1767707 diagnostic and 1060 screening Date of Patient Navigator/DERS=August 2003	Patient navigator/DERS (direct endoscopic referral system) intervention vs no navigator	Broken appointment rates, coverage screening colonoscopy, rate of screening colonoscopies	**Characteristic of person receiving screening colonoscopies** <u>Tot, average n per month</u> Before intervention=56.8 After intervention=119.0 <u>Navigator, %</u> No: before vs after=90 vs 55 Yes: before vs after=10 vs 45 **Estimate coverage for screening colonoscopy** (monthly target for each Zip Codes) Before intervention=5.2 After intervention=15.6 (RR=3.0, 95%CI=1.9-4.7) Immediately following the introduction of the patient navigators, there was a dramatic and sustained decline in the **broken appointment rates** for both screening and diagnostic colonoscopy (from 67% in May of 2003 to 5% in June of 2003). The likelihood of keeping the appointment for colonoscopy after the patient navigator intervention increased by nearly 3-fold (relative risk = 2.6, 95% CI 2.2–3.0)	**III** In an urban public hospital setting, a multi-faceted intervention led to marked increases in screening colonoscopy rates and thereby improved potential for earlier detection of malignant and pre-malignant disease in the surrounding community, which ultimately should lead to a decrease in colorectal cancer deaths. Future research and interventions should seek to assess and address individual and neighborhood level barriers to timely colorectal cancer screening.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; non exposed cohort drawn from the same community as the exposed cohort. Ascertainment of exposure**:** secure record; adjustment for multiple prognostic factor. Assessment of outcome by record linkage.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Nease D.E., 2008	To examining whether a generalisable reminder system could produce increased CRC screening rates, we also sought to understand the impact of practices' organisational contexts. Prospective cohort study USA	Patients from 12 community practices located in Michigan. Random sample of 50 female and 50 male CRC screening patients in each practice who had visited the practice during the study period. All practices provided an electronic data file of their patients aged 50 or older for population of their ClinfoTracker system. Study period :9 months	ClinfoTracker as computer reminder system for CRC screening	CRC Screening rates	**Baseline screening rates (12 practice**) = average 41.7% (range 24.1-59.6%) **9 month CRC screening rates** average 66.5% (range 33.2-66.5% **Increase on average**: 9% (range 9-24%) p=0.002 **Impact of technology and cohesion factors** High technology practices=74 Low technology practices=45% p=0.01 **Mean CRC screening rate changes in practice by organisational cohesion** Low (n=8)=7.9 (difference for all "low cohesion" practices: p=0.026) High (n=4)=15.3 **Mean CRC screening rate changes in practice by technology adoption** Low (n=8)=13.3 (difference for all "low technology" practices: p=0.004) High (n=4)=8.0 (difference for all "high technology" practices: p=ns)	**III** Implementing a generalisable CRS in diverse primary care practices yielded significant improvements in CRC screening rates. Technology capabilities are important in maintaining the system, but practice cohesion may have a greater influence on screening rates. This work has important implications for practices implementing reminder systems.

Quality assessment: population truly representative of the people at average risk of colorectal cancer in the community; Ascertainment of exposure**:** secure record; Assessment of outcome by record linkage.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Percac-Lima S., 2008	To evaluate a culturally tailored intervention to increase CRC screening, primarily using colonoscopy, among low income and non-English speaking patients. Randomised controlled trial USA	1,223 patients (mean age 63 years; 60% female) from a single, urban community health center serving a low-income, ethnically diverse population, aged 52-79 years who had not undergone CRC screening. Patients were randomised to intervention group (n=409) or usual care control group (n=814). No difference in demographic characteristics between intervention and usual care groups. Study period=9 months	Culturally tailored navigator program for CRC screening: Intervention group= Intervention patients received an introductory letter with educational material followed by phone or in-person contact by a language-concordant "navigator." Navigators (n=5) were community health workers trained to identify and address patient reported barriers to CRC screening. Individually tailored interventions included patient education, procedure scheduling, translation and explanation of bowel preparation, and help with transportation and insurance coverage (n=409; mean age 63.1±7.7; 58 female) Control group=usual care (n=814; mean age 62.9±7.8; 61% female)	Rates of colorectal cancer screening	**Incidence CRC screening, %** I vs C= 27.4 vs 11.9 p<0.001 **% patients completing colonoscopy** I vs C= 20.8 vs 9.69 p<0.001 The navigator program showed a relatively larger effect in females, older patients, non-Latinos, English speakers, and those without private insurance when comparing intervention vs. usual care patients. (Among patients contacted by the navigator n=302) **% patients completing CRC screening** those contacted in person vs those contacted by other methods =42.7% vs. 33.0%, p=0.09 **% patients completing colonoscopy** those contacted in person vs those contacted by other methods =35.0% vs. 23.2%, p=0.03 Almost all patients had at least one barrier identified, and most had several (mean=44, median=4.0).	**II** A culturally tailored, language concordant navigator program designed to identify and overcome barriers to colorectal cancer screening can significantly improve colonoscopy rates for low income, ethnically and linguistically diverse patients.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Powe B.D., 2004	To evaluate the effectiveness of a multiphasic culturally relevant intervention regimen, delivered at established intervals over a 12-month period on knowledge of colorectal cancer and rates of participation in FOBT among elders who attend community-based senior centers in a Southeastern state. Randomised controlled trial USA	134 (mean age 73.83±8.88 years; 88% female) men and women aged 50 and older from 15 senior centers. The 15 centers were randomly selected and assigned to the Cultural and Self-Empowerment Group (n=5) who received the full five phases (video, calendar, poster, brochure, and flier), the Modified Cultural Group (n=5) who received only one phase of the intervention (video), and the Traditional Group (n=5) who served as the control group (standard treatment). Data collected at 3 time periods: at baseline, 6 months after baseline, at 12 months after baseline.	Strategies to promote colorectal cancer knowledge and screening: Cultural and self-empowerment = participants were assigned to received video, an educational calendar, poster, brochure and flier (n=54; female 82%). Modified cultural = participants received only video (n=39; female 92%) Traditional = standard treatment(n=41; female 93%)	Knowledge of colorectal cancer,	**Knowledge of colorectal cancer-baseline, mean± sd** Cultural and self-empowerment: 8.74±1.81 Modified cultural: 7.94±1.60 Traditional: 8.63±2.02 Tot sample: 8.47±1.84 **Knowledge of colorectal cancer-6 months, mean± sd** Cultural and self-empowerment: 8.70±1.89 Modified cultural: 8.58±1.71 Traditional: 8.70±1.66 Tot sample: 8.67±1.76 **Knowledge of colorectal cancer-12 months, mean± sd** Cultural and self-empowerment: 9.12±1.75 Modified cultural: 8.20±1.71 Traditional: 8.31±1.98 Tot sample: 8.61±1.85 **FOBT screening participation, n (%)** Cultural and self-empowerment: 33 (61) Modified cultural: 18 (46) Traditional: 5 (15)	**II** The model suggests that persons with greater knowledge of colorectal cancer may have higher rates of participation in colorectal cancer screening.. Knowledge cancer increased significantly for the participants in the Cultural and Self- Empowerment Group who received a 5-phase intervention delivered over a 12-month period compared to the other two groups. This group also had a higher rate of participation in FOBT. In fact, group membership and knowledge of colorectal cancer were the only significant predictors of participation in FOBT for this sample. This finding supports the premise of the PFM and supports the fact that educational interventions that are tailored to meet the populations' learning needs, are culturally appropriate, and are delivered using multiple strategies delivered over an extended time period can be successful in increasing knowledge of colorectal cancer. This fact has clinical significance as well.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Rubin D.T, 2007	To determine patient retention of information communicated after outpatient endoscopic procedures and to evaluate the effectiveness of a standard computer-generated endoscopy report (WR) in enhancing this patient knowledge. Randomised controlled trial (double-blind) USA	80 consecutive outpatients who presented to 3 endoscopists were randomised to receive the results of their upper or lower endoscopy via standard verbal report (VR) or by standard VR followed by receipt of a computer-generated endoscopy report (VR+WR) from the Olympus ImageManager report generator. The endoscopist communicated the VR after a standard postprocedure recovery period of 30 to 60 minutes and routinely discussed all findings and recommendations as mentioned in the WR. Recall of the endoscopic procedure was assessed by using a piloted 11-question survey instrument to be filled out 3 days after the procedure. No statistical difference between groups age and sex.	Way to communicate results after endoscopy: VR group= standard verbal report (n=39; mean age 58.5±13.5; female 65%) VR+WR group = standard VR followed by receipt of a computer-generated endoscopy report (n=39; mean age 57.5±16.7; female 72%)	Composite score (number of correct survey responses of 10); recall of endoscopic procedure	**Question about who performed the procedure, %** VR group=74 VR+WR group=97 p=0.026 **Question about what recommendation were made, %** VR group=42 VR+WR group=72 p=0.026 **Composite score** VR group=8.9/10 VR+WR group=7.7/10 p=0.003	**II** A computer-generated endoscopy report (WR) significantly improved patient recall of endoscopic procedure information compared with a VR alone. Despite this, patients were unable to recall 28% of recommendations. Additional study to determine if such enhanced physician-patient communication improves patient satisfaction or follow-up, and whether more specific patient-directed results further improve recall needs to occur.

Quality assessment: allocation concealment: unclear; blindness of endoscopist: yes; blindness of patients: yes; blindness of outcome assessor: no; 78 agreed to participate; lost at follow up: 60/78 returned survey.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Sequist T.D., 2009	To compare the individual and joint impact of personalized mailings to patients and electronic reminders to primary care physicians to promote colorectal cancer screening within a multisite group practice. Randomised controlled trial USA	21,860 patients aged 50 to 80 years who were overdue for colorectal cancer screening and 110 primary care physicians. Patients were randomly assigned to receive mailings containing an educational pamphlet, faecal occult blood test kit, and instructions for direct scheduling of flexible sigmoidoscopy or colonoscopy or no intervention. Physicians were randomly assigned to receive electronic reminders during office visits with patients overdue for screening or no intervention. Survey for 43 (of 55 in the electronic reminder intervention) physician. No difference about age and gender according to intervention status.	Personalized mailing to patients and electronic reminder to primary care physicians to promote CRC screening: Patient mailing intervention: patients were randomised to received no intervention (control group= 10930; mean age 60.4±8.4; 57% female) or to receive mailings containing an educational pamphlet, faecal occult blood test kit, and instructions for direct scheduling of flexible sigmoidoscopy or colonoscopy (intervention group= 10930; mean age 60.5±8.3; 56.8% female) Physician reminder intervention: 55 physicians were randomised to receive no intervention (control group= 10948; mean age 60.5±8.4; 59.8% female) and 55 physicians to receive electronic reminders during office visits with patients overdue for screening (intervention group= 10912; mean age 60.3±8.3; 54% female)	Completion of 1 of the following 3 options during the 15-month study period.	**Completed CRC screening by patient mailing intervention, %** All patients Intervention= 44.0 Control= 38.1 $p<0.001$ The impact of the mailing did not differ between women and men but was more effective among older patients (absolute increase in screening rates ranging from 3.7% among patients aged 50 to 59 years to 10.1% among patients aged 70 to 80) Among patients with ≥3 primary care visits Intervention= 59.5 Control= 52.3 $p<0.001$ **Completed CRC screening by physician reminder intervention, %** All patients Intervention= 41.9 Control= 40.2 $p=0.47$ Among patients with ≥3 primary care visits Intervention= 59.5 Control= 52.7 $p=0.07$ **Interaction between patient intervention and physician intervention**= -0.6%; 95%CI: -1.02-0.1%	II Mailed reminders to patients are an effective tool to promote colorectal cancer screening, and electronic reminders to physicians may increase screening among adults who have more frequent primary care visits.

Quality assessment: allocation concealment: unclear; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; none lost at follow up.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Thompson N.J, 2000	To test the impact of authorizing support staff to order faecal occult blood tests in a general internal medicine clinic organized into four teams. Randomised controlled trial (quasi-experimental) USA	1,109 patients aged 50-69 years scheduled to see a primary provider between 2 months were randomised to treatment group (n=545) and control group (n=564). No difference about age and gender between treatment and control group	Support- staff intervention for FOBT screening: <u>Treatment group</u>: licensed practical nurses (LPNs) were authorized to order faecal occult blood tests for these patients and give them before they left the clinic. (n=545; mean age 60.4±5.9; 98% male) <u>Control group</u>: usual order (n=564; mean age 60.1±6.1; 98% male)	FOBT ordering and returning	**FOBT kit orders, %** <u>Baseline: 1 year before intervention</u> Treatment= 10 Control= 9 p=0.605 <u>Intervention time period for all patients</u> Treatment= 52 Control=15 p=0.001 <u>Intervention time period for eligible patients</u> Treatment= 72 Control=19 p=0.001 **FOBT cards returned, %** <u>Baseline: 1 year before intervention</u> Treatment= 47 Control= 52 p=0.546 <u>Intervention time period for all patients</u> Treatment= 44 Control=48 p=0.571 <u>Intervention time period for eligible patients</u> Treatment= 46 Control=43 p=0.605 **Multivariate regression models comparing treatment and control group on ordering the FOBT:** in all models (no covariates; n diagnoses; n diagnoses, provider coverage; n of diagnoses, provider coverage, age, gender) the association between intervention and frequency of FOBT ordering is quite strong and statistically significant. **Multivariate regression models comparing treatment and control group on returning the FOBT:** the association between intervention and return of FOBT is not significant.	**II** Delegation, supported by use of decision-support algorithms, can dramatically increase the rate at which a preventive service is offered to patients without decrement in the rate at which the patient returns the FOBT samples.

Quality assessment: allocation concealment: inadequate (firm system); blindness of provider: no; blindness of patients: no; blindness of outcome assessor: yes; sample of 1109 of the 1123 patients who presented to the clinic and met the inclusion criteria because 14 excluded from the analysis.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Trevena LJ, 2008	To test the effect of a self administered DA (decision aids compatible with 'at-home' testing) on informed choice in participants from a range of educational backgrounds, and to assesses whether their decisions are consistent with values about screening (i.e. 'integrated' decision-making). Randomised controlled trial USA	314 people aged 50-74 years from six primary care locations without an FOBT, sigmoidoscopy or colonoscopy in the previous two years were randomised to receive by post, the age-gender-family history specific DA (decision aid group=1547) or the Australian Government's consumer guidelines on FOBT screening ()guidelines groups=157) along with a self-administered questionnaire.	Decision aids booklet vs guidelines Decision aids group= self-administered decision aid (DA) booklet about outcomes of biennial faecal occult blood testing (FOBT) screening. Information was presented according to best evidence using words and 1000-face diagrams.12 The booklet was 20 pages long. Participants were mailed the relevant booklet for their age and gender and a questionnaire which they were asked to complete and return (n=157; 40.8% male). Guidelines group= guidelines consisted of three pages of text with information recommending biennial FOBT for people over the age of 50, to reduce mortality from colorectal cancer. It contained very minimal information about false-positives and none about the risks of follow-up colonoscopy testing. There was no quantification of outcomes apart from an unreferenced statement that up to 80–90% of colorectal cancer could be detected through FOBT screening (n=157; 40.8% male).	FOBT uptake, informed choice and integrated decision	**Effect of DA on screening decision** (DA group (n=134) vs guidelines group (137)) **Integrated knowledge and values, n (%)** DA group=14 (10.4) Guidelines group =2 (1.5) $p=0.002$ **Adequate Knowledge/informed, n (%)** DA group=28 (20.9) Guidelines group =8 (5.8) $p=0.0001$ **Intention to screen, n (%)** DA group=117 (87.3) Guidelines group =124 (90.5) $p=0.40$ **Clear values, n (%)** DA group=83 (61.9) Guidelines group =81 (59.1) $p=0.63$ **FOBT uptake, %(after 1 month)** DA group=5.2 Guidelines group =6.6 $p=0.64$	**II** Detailed absolute risk and benefit information about FOBT screening can be effectively used at home by people to increase informed choice. The DA was effective in people with lower education levels.

Quality assessment: allocation concealment: adequate; blindness of provider: yes; blindness of patients: no; blindness of outcome assessor: yes; lost at follow up: self-administered questionnaire completed=134/157 in decision aid group; self-administered questionnaire completed=137/157 in guidelines group; follow up phone interview at 1 month in DA group=133/134;; follow up phone interview at 1 month in DA group=136/134.

Author, publication year	Study Objective Study design	Study Participants	Intervention	Outcomes	Results	Conclusion Levels of evidence
Turner B.J 2008	To compare peer coach telephone support with mailed professional brochures about colorectal cancer screening in improving compliance with a first scheduled colonoscopy; to compare colonoscopy attendance for persons receiving these interventions to attendance of concurrent patients who did not receive additional support. Randomised controlled trial USA	275 consecutive patients aged 50 years and older (mean age 60.7; 69.1% female) who kept <75% of visits to 4 primary care practices and scheduled for a first colonoscopy from February 12005 to August 2006. Patients were randomised in blocks of 6 to peer coach support (peer coach group) or to mailed brochures about CRC screening. (brochure group). Compared with the other patient groups, the peer coach group was more likely to be black, Medicaid insured, and have low primary care visit compliance.	Colonoscopy support intervention: Peer coach group: patients received a phone call by a peer coach trained (5 older patients who had had a colonoscopy)within 2 weeks of the colonoscopy appointment to address barriers to attendance(n=70) Brochure group: patients received 2 brochures which offer patient-oriented information about the reasons for screening, risk factors, benefits, and various screening modalities, especially colonoscopy (n=66) No intervention group: no supported needed (n=49); no contacted (n=49), refused intervention study (n=41)	Colonoscopy attendance	**Colonoscopy attendance, %** Overall =64.0 By intervention group peer coach=68.6 Brochure =57.6 Peer coach vs brochure: 2.04 (95%CI=0.93-4.45) No intervention group No support needed=81.6 Failed contact =61.2 Refused support=48.8 **Adjusted OR of colonoscopy attendance among all subjects (n=275), OR (95% CI) p** Patient study group Brochure= 1.0 Peer coach=2.14 (0.99-4.63) p=0.05 No support needed=2.68 (1.05-6.83) p=0.04 Failed contact=0.85 (0.36-2.02) p=0.71 Refused support=0.61 (0.26-1.45) p=0.27	II For patients who often fail to keep appointments, peer coach support appears to promote colonoscopy attendance more than an educational brochure.

Quality assessment: allocation concealment: inadequate; blindness of provider: no; blindness of patients: no; blindness of outcome assessor: none lost at follow up.

List of key clinical questions

Ch.		Clinical question	Page	Sect.
1	1	Is FOBT screening offered to the general population age 50 and older effective in reducing colorectal cancer mortality and overall mortality?	E-13	1.1.1
1	2	Is immunochemical FOBT (I-FOBT) superior to guaiac FOBT (G-FOBT) in its test performance characteristics (sensitivity and specificity)?	E-23	1.2.1
1	3	Which is the best time interval for offering screening by guaiac FOBT testing?	E-43	1.3.1
1	4	Which is the best time interval for offering screening by immunochemical FOBT?	E-43	1.3.1
1	5	Is flexible sigmoidoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?	E-49	1.4.1
1	9	Is colonoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?	E-49	1.4.1
1	6	Which is the best time interval for offering screening by flexible sigmoidoscopy?	E-64	1.5.1
1	7	Which is the optimal age range in which to perform screening with FS (at younger age lesions in the distal bowel more frequent, at older age are lesions in the proximal bowel more frequent)?	E-68	1.6.1
1	11	Which is the optimal age range in which to perform screening with colonoscopy (at younger age are lesions in the distal bowel more frequent, at older age are lesions in the proximal bowel more frequent)?	E-68	1.6.1
1	8	Are combined tests (FOBT and flexible sigmoidoscopy) more effective than single tests (only FOBT or only flexible sigmoidoscopy)?	E-76	1.7.1
1	10	Which is the best time interval for offering screening by colonoscopy?	E-84	1.8.1
1	12	Is CT colonography screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?	E-94	1.9.1
1	12b	Is CT colonography comparable to colonoscopy in test performance characteristics (sensitivity and specificity)?	E-94	1.9.1
1	13	Is capsule endoscopy screening offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?	E-116	1.10.1
1	13b	Is capsule endoscopy comparable to colonoscopy in test performance characteristics (sensitivity and specificity)?	E-116	1.10.1
1	14a	Is guaiac FOBT screening offered to the general population age 50 and older cost-effective?	E-121	1.11.1
1	14b	Is immunological/immunochemical FOBT screening offered to the general population age 50 and older cost-effective?	E-121	1.11.1
1	14c	Is flexible sigmoidoscopy screening offered to the general population age 50 and older cost-effective?	E-121	1.11.1
1	14d	Is colonoscopy screening offered to the general population age 50 and older cost-effective?	E-122	1.11.1
1	17	Which is the best age range for offering screening by GUAIAC testing?	E-136	1.12.1
1	17b	Which is the best age range for offering screening by immunological/immunochemical testing?	E-136	1.12.1

Ch.		Clinical question	Page	Sect.
1	18	Is DNA stool testing offered to the general population age 50 and older effective in reducing colorectal cancer incidence or mortality?	E-140	1.13.1
1	18b	Is stool DNA comparable to guaiac / immunochemical FOBT in its test performance characteristics (sensitivity and specificity)?	E-140	1.13.1
1	19	What is the rate of negative side effects of guaiac FOBT screening?	E-149	1.14.1
1	20	What is the rate of negative side effects of immunological FOBT screening?	E-149	1.14.1
1	21	What is the rate of negative side effects of flexible sigmoidoscopy screening?	E-149	1.14.1
1	22	What is the rate of negative side effects of colonoscopy screening?	E-150	1.14.1
1	23	Is immunochemical FOBT screening offered to the general population age 50 and older effective in reducing colorectal cancer mortality?	E-157	1.15.1
2	1	Is organised screening for colorectal cancer offered to the asymptomatic general population age 50 years and older more effective than non organised screening (opportunistic screening or case finding) in reducing colorectal cancer incidence and mortality and in improving coverage and equity?	E-181	2.1.1
2	2	Are public information campaigns for organised and non-organised colorectal cancer screening offered to asymptomatic general population aged 50 years and older effective in improving uptake and equity?	E-202	2.2.1
2	3	Which strategy is more effective in improving coverage and equity?	E-202	2.2.1
2	4	Which are the barriers which limit participation in screening programmes?	E-207	2.3.1
2	5	Are there effective interventions to reduce barriers to participation?	E-222	2.4.1
2	6	Which active invitation strategy is more effective in improving participation in colorectal cancer screening among the general asymptomatic population age 50 years and older ?	E-232	2.5.1
2	7	Is active invitation of not yet covered asymptomatic people eligible for colorectal cancer screening effective and cost effective in improving coverage, and equity in access?	E-264	2.6.1
2	8	Which characteristics of family history for colorectal cancer are necessary to assign people to the screening protocols different from the strategy adopted for the average risk population?	E-269	2.7.1
2	9	Is active invitation to diagnostic assessment more effective than spontaneous presentation in improving the proportion of positives undergoing necessary assessment?	E-280	2.8.1
2	10	Which strategy to invite positive patients to undergo diagnostic assessment is more effective in improving detection rate and the proportion of positive undergoing necessary assessment?	E-280	2.8.1
2	11	Are strategies aimed at soliciting positive patients who are non responders to diagnostic assessment effective and cost effective in improving further investigations, detection rate?	E-280	2.8.1
2	12	Does dietary restriction needed to perform guaiac FOBT or multiple sampling reduce participation compared to FOBtesting which do not need any restriction?	E-286	2.9.1

Ch.		Clinical question	Page	Sect.
2	13	Do different kinds or location of bowel preparation for FS reduce participation?	E-293	2.10.1
3	1	What early performance indicators were used for if monitoring CRC screening programmes, in trials or in other screening programmes?	E-319 E-326	3.1.1 3.2.1
3	2	What are the coverage and participation rates achieved in studies of CRC screening using FOBT (guaiac/immunology),or using flexible sigmoidoscopy or colonoscopy?	E-319 E-326	3.1.1 3.2.1
3	3	What are the detection-rates of cancers/adenomas achieved in studies of CRC screening using FOBT (guaiac/immunology), flexible sigmoidoscopy, or colonoscopy?	E-319 E-327	3.1.1 3.2.1
3	4	What are the positive rates achieved in studies of CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy?	E-320 E-327	3.1.1 3.2.1
3	5	What is the uptake of colonoscopy achieved in studies of CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy ?	E-320 E-328	3.1.1 3.2.1
3	6	What proportion of screen detected cancers achieved in studies of CRC screening is stage I or II, based on TNM classification, for CRC screening using FOBT(guaiac/immunology), or flexible sigmoidoscopy?	E-320 E-328	3.1.1 3.2.1
3	7	What are the positive predictive values of the screening test using FOBT (guaiac/immunology), or flexible sigmoidoscopy for cancer/ precancer lesions achieved in studies of CRC screening?	E-320 E-329	3.1.1 3.2.1
3	8	What are the rates of adverse effects (deaths within 30 days / early bleeding / perforation) of screening colonoscopy or a colonoscopy following a positive test observed within a CRC screening programme using FOBT(guaiac/immunology), or flexible sigmoidoscopy?	E-321	3.1.1
3	9	What are the rates of inadequate tests using FOBT (guaiac/immunology), flexible sigmoidoscopy or colonoscopy achieved in studies of CRC screening?	E-321 E-329	3.1.1 3.2.1
3	10	What are the rates of incomplete screening colonoscopies and sigmoidoscopies and follow-up colonoscopies?	E-321 E-329	3.1.1 3.2.1
3	11	What is the proportion of benign lesions referred for surgery?	E-321	3.1.1
3	12	What is the proportion of malignant adenomas endoscopically treated?	E-322	3.1.1
3	19	What is the rate of negative side effects of guaiac FOBT screening?	E-342	3.4.1
3	20	What is the rate of negative side effects of immunological FOBT screening?	E-342	3.4.1
3	21	What is the rate of negative side effects of flexible sigmoidoscopy screening?	E-342	3.4.1
3	22	What is the rate of negative side effects of colonoscopy screening?	E-342	3.4.1
4	1	Do different sampling techniques change FOBT screening uptake and/or compliance?	E-359	4.1.1
4	2	What evidence is there that the method of test distribution /collection changes uptake /compliance?	E-364	4.2.1
4	3	What test/test kit features/laboratory testing arrangements improve the reliability of test measurement?	E-371	4.3.1

Ch.		Clinical question	Page	Sect.
4	4	What laboratory quality assurance/external quality assessment/quality internal control procedures have been described in the literature?	E-375	4.4.1
4	5	What is the impact on clinical performance of different testing algorithms?	E-377	4.5.1
4	6	What is the impact on clinical performance of modifying the test cut-off limit?	E-388	4.6.1
4	7	What is the quantitative impact of diet and/or drugs on test results and/or clinical performance?	E-403	4.7.1
4	8	What is known about the effect of the time between sample collection and testing and the method of storage and transport on the reliability of the test result and the positivity rate?	E-414	4.8.1
5	3	Which variables, that need to be identified before the examination, are associated with an increased risk of side-effects or adverse events in FS or colonoscopy?	E-441	5.1.1
5	12	Is there evidence linking poor performance of colonoscopy with adverse outcomes for patients?	E-442	5.1.1
5	4	What regimens and schedules provide an optimal bowel preparation for FS and colonoscopy, with minimal side effects and patient discomfort?	E-462	5.2.1
5	5	What is the difference in terms of quality (diagnostic yield), cost and side effects of short vs longer scopes for FS screening?	E-475	5.3.1
5	6	Do the following modalities improve completion rates in lower GI endoscopy: • Variable stiffness instruments, • MR tracking devices, • Wire guided techniques	E-481	5.4.1
5	7	Do the following modalities improve high risk lesion detection rates in lower GI endoscopy: • dye spraying, • NBI, • autofluorescence	E-487	5.5.1
5	8	Does carbon dioxide insufflation improve patient tolerance and reduce complications?	E-509	5.6.1
5	9	What are the benefits and risks of conscious versus deep sedation?	E-517	5.7.1
5	13	What are the key performance indicators for a technically sound, high quality and safe procedure?	E-547	5.8.1
5	14	What is the most reliable method used to identify completeness of colonoscopy?	E-550	5.9.1
5	15	What defines a complete examination of FS (up to splenic flexure)? Does the imager improve the determination of completeness?	E-551	5.10.1
6	1	What are the professional and training requirements for primary care physicians?	E-581	6.1.1
6	2	What are the professional and training requirements for endoscopists?	E-582	6.1.1
6	3	What are the professional and training requirements for radiologists?	E-583	6.1.1
6	4	What are the professional and training requirements for pathologists?	E-583	6.1.1

Ch.		Clinical question	Page	Sect.
6	5	What are the professional and training requirements for surgeons?	E-584	6.1.1
6	6	What are the professional and training requirements for laboratory staff?	E-584	6.1.1
6	7	What are the professional and training requirements for administrative and clerical staff?	E-584	6.1.1
6	8	What are the professional and training requirements for nurses?	E-585	6.1.1
6	9	What are the professional and training requirements for public health specialists?	E-585	6.1.1
7	1	Does the use of the Vienna classification improve the diagnostic reproducibility of assessment of colorectal neoplastic lesions?	E-605	7.1.1
7	2	What are the levels of diagnostic reproducibility of the pathological features: dysplasia and villousness in colorectal adenomas?	E-610	7.2.1
7	3	What is the actual proportion of high grade dyspasia (HGD), villousness, size >10 mm in flexible sigmoidoscopy/ FOBT/colonoscopy studies?	E-615	7.3.1
7	4	Are there significant differences in the detection rates of non polypoid colorectal neoplasms (flat adenomas, depressed adenomas, lateral spreading tumours) among the different types of screening programmes (FOBT vs. FS vs. colonoscopy)?	E-627	7.4.1
7	5 and 6	In T1 adenocarcinoma what is the importance of site of the primary tumour and which of the following pathologic features best predict lymph node metastasis or local recurrence for management decisions (surgery vs. surveillance) of cancerized adenomas? Which are the levels of reliability and diagnostic reproducibility of these pathologic features? • incomplete excision (if yes, 0mm or 1mm or 2mm) • lymphatic invasion • vascular invasion • poor differentiation/high grade • budding of glands on invasive border (tumour budding)	E-636	7.5.1
7	7	What is the evidence that external quality assurance programmes decrease the variability of reporting of pathology in • colorectal cancer • breast cancer • other tumours	E-661	7.6.1
7	8	Is there evidence for a minimum number of specimens that a pathologist should report in a screening programme for • adenomas • colorectal cancer resections	E-668	7.7.1
7	9	Is there evidence that proforma reporting improves the quality of a screening programme, or reporting of colorectal cancer?	E-676	7.8.1
7	10	Do different modalities of advanced polyp measurement (endoscopic measurement vs. pathologist's measurement before and after fixation, slide preparation) affect diagnostic reproducibility and the detection rate of advanced adenomas in a screening setting?	E-691	7.9.1
7	11	What is the currently available evidence on sessile serrated polyps, serrated adenomas, and hyperplastic polyp management?	E-697	7.10.1
8	1	How should polyps be treated (criteria for endoscopic or surgical removal)?	E-709	8.1.1

Ch.		Clinical question	Page	Sect.
8	2	How should malignant polyps (T1 – carcinomas) be treated (criteria for completion surgical resection)?	E-732	8.2.1
8	3	Treatment of rectal adenoma and T1 cancer by transanal endoscopic microsurgery (TEM)	E-751	8.3.1
8	4	How should other screen detected cancers be treated?	E-763	8.4.1
8	5	How should incomplete adenoma excision be managed ?	E-771	8.5.1
8	6	Which are patient-related criteria for postponing polypectomy in asymptomatic people undergoing CRC screening and taking anticoagulants/antiaggregants?	E-775	8.6.1
8	7	Is there any difference in complication (bleeding) and quality of sample between cold snare and hot biopsy for removal of small polyps (<1 cm)?	E-787	8.7.1
8	8	What is the efficacy of radiotherapy for T1 rectal cancer after local excision?	E-795	8.8.1
9	1	What is the risk of neoplasia after a negative colonoscopy?	E-813	9.1.1
9	2	What is the risk of neoplasia after removal of hyperplastic polyps?	E-816	9.2.1
9	3	What is the yield of FOBT after removal of adenomas?	E-817	9.3.1
9	4	What is the rate of neoplasia after endoscopic removal of adenomas?	E-818	9.4.1
9	5	How is the rate of recurrence influenced by the characteristics of the adenoma removed (size, histology, number, dysplasia, location)?	E-822	9.5.1
9	6	What is the optimal time interval between surveillance colonoscopies?	E-831	9.6.1
9	7	What is the risk of neoplasia after local removal of a low-risk malignant polyp (T1 –carcinoma)?	E-833	9.7.1
9	8	Which are appropriate quality indicators and standards to evaluate surveillance after polypectomy?	E-834	9.8.1
10	1	What are the currently available strategies used for communicating information about colorectal cancer screening to the general public?	E-891	10.1.1
10	2	What are the currently available strategies used for educating or supporting health professionals for providing information about CRC screening to the general public?	E-891	10.1.1
10	3	What quality indicators are currently used to evaluate the effectiveness of communicating information to the general public concerning CRC screening?	E-892	10.1.1

Appendix 2

Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC)

COUNCIL RECOMMENDATION
of 2 December 2003
on cancer screening

(2003/878/EC)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4), second subparagraph, thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Whereas:

(1) Article 152 of the Treaty provides that Community action is to complement national policies and be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

(2) Further development of cancer screening programmes should be implemented in accordance with national law and national and regional responsibilities for the organisation and delivery of health services and medical care.

(3) Cancer is a major disease and cause of death throughout Europe, including the future Member States. An estimated number of 1 580 096 new cancer cases, excluding non-melanoma skin cancer, occurred in the European Union in 1998. Of these, 1,4 % were cervical cancers, 13 % breast cancers, 14 % colorectal cancers and 9 % prostate cancers. Cervical and breast cancer constituted 3 % and 29 %, respectively, of new cancers in women. Prostate cancer constituted 17 % of new cancers in men.

(4) Principles for screening as a tool for the prevention of chronic non-communicable diseases were published by the World Health Organisation in 1968 and by the Council of Europe in 1994. These two documents form, together with the current best practice in each of the cancer screening fields, the basis for the present recommendations.

(5) Additionally, these recommendations are based on the 'Recommendations on cancer screening' of the Advisory Committee on Cancer Prevention together with the experience gathered under the different actions sustained under the Europe against Cancer programme where European collaboration has helped, for example, high quality cancer screening programmes to provide efficient European guidelines of best practice and to protect the population from poor quality screening.

(6) Important factors which have to be assessed before a population-wide implementation is decided upon include, *inter alia*, the frequency and interval of the application of the screening test as well as other national or regional epidemiological specificities.

(7) Screening allows detection of cancers at an early stage of invasiveness or possibly even before they become invasive. Some lesions can then be treated more effectively and the patients can expect to be cured. The main indicator for the effectiveness of screening is a decrease in disease-specific mortality. As in the case of cervical cancer, cancer precursors are detected, a reduction in cervical cancer incidence can be considered a very helpful indicator.

(8) Evidence exists concerning the efficacy of screening for breast cancer and colorectal cancer, derived from randomised trials, and for cervical cancer, derived from observational studies.

(9) Screening is, however, the testing for diseases of people for which no symptoms have been detected. In addition to its beneficial effect on the disease-specific mortality, screening can also have negative side effects for the screened population. Healthcare providers should be aware of all the potential benefits and risks of screening for a given cancer site before embarking on new population-based cancer screening programmes. Furthermore, for the informed public of today, these benefits and risks need to be presented in a way that allows individual citizens to decide on participation in the screening programmes for themselves.

(10) Ethical, legal, social, medical, organisational and economic aspects have to be considered before decisions can be made on the implementation of cancer screening programmes.

(11) Due account should be taken of specific needs of persons who may be at higher cancer risk for particular reasons (e.g. biological, genetic, lifestyle and environmental, including occupational).

(12) The public health benefits and cost efficiency of a screening programme are achieved if the programme is implemented systematically, covering the whole target population and following best-practice guidelines.

(13) The cost-effectiveness of cancer screening depends on several factors such as epidemiology, and healthcare organisation and delivery.

(14) Systematic implementation requires an organisation with a call/recall system and with quality assurance at all levels, and an effective and appropriate diagnostic, treatment and after-care service following evidence-based guidelines.

(15) Centralised data systems, including a list of all categories of persons to be targeted by the screening programme and data on all screening tests, assessment and final diagnoses, are needed to run organised screening programmes.

(16) All procedures for collecting, storing, transmitting and analysing data in the medical registers involved must be in full compliance with the level of protection referred to in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (¹), as well as in full compliance with the relevant provisions of Member States on the management and processing of health data in accordance with Article 8 of the Directive.

(17) Quality screening includes analysis of the process and outcome of the screening and rapid reporting of these results to the population and screening providers.

(18) This analysis is facilitated if the screening database can be linked to cancer registries and mortality databases.

(19) Adequate training of personnel is a prerequisite for high quality screening.

(20) Specific performance indicators have been established for cancer screening tests. These should be monitored regularly.

(¹) OJ L 281, 23.11.1995, p. 31.

(21) Adequate human and financial resources should be available in order to assure the appropriate organisation and quality control in all the Member States.

(22) Action should be taken to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

(23) It is an ethical, legal and social prerequisite that cancer screening should only be offered to fully informed people with no symptoms if the screening is proved to decrease disease-specific mortality, if the benefits and risks are well known, and if the cost-effectiveness of the screening is acceptable.

(24) The screening methods which presently meet these strict prerequisites are listed in the Annex.

(25) No screening test other than those listed in the Annex is scientifically justified to be offered to people with no symptoms in an organised population-based programme before it has been shown in randomised controlled trials to decrease disease-specific mortality in particular.

(26) The screening tests listed in the Annex can only be offered on a population basis in organised screening programmes with quality assurance at all levels, if good information about benefits and risks, adequate resources for screening, follow-up with complementary diagnostic procedures and, if necessary, treatment of those with a positive screening test are available.

(27) The introduction of the recommended screening tests in the Annex, which have demonstrated their efficacy, should be seriously considered, the decision being based on available professional expertise and priority-setting for healthcare resources in each Member State.

(28) Once there is evidence that a new screening test is effective, evaluation of modified tests may be possible using other epidemiologically validated surrogate endpoints if the predictive value of these endpoints is established.

(29) Screening methodologies are subject to ongoing development. The application of recommended screening methodologies should therefore be accompanied by simultaneous assessments of the quality, applicability and cost-effectiveness of new methods if available epidemiological data justify this. In fact, the ongoing work may lead to new methods, which could ultimately replace or complement the tests listed in the Annex or be applicable to other types of cancer.

HEREBY RECOMMENDS THAT MEMBER STATES:

1. Implementation of cancer screening programmes

(a) offer evidence-based cancer screening through a systematic population-based approach with quality assurance at all appropriate levels. The tests which should be considered in this context are listed in the Annex;

(b) implement screening programmes in accordance with European guidelines on best practice where they exist and facilitate the further development of best practice for high quality cancer screening programmes on a national and, where appropriate, regional level;

(c) ensure that the people participating in a screening programme are fully informed about the benefits and risks;

(d) ensure that adequate complementary diagnostic procedures, treatment, psychological support and after-care following evidence-based guidelines of those with a positive screening test are provided for;

(e) make available human and financial resources in order to assure appropriate organisation and quality control;

(f) assess and take decisions on the implementation of a cancer screening programme nationally or regionally depending on the disease burden and the healthcare resources available, the side effects and cost effects of cancer screening, and experience from scientific trials and pilot projects;

(g) set up a systematic call/recall system and quality assurance at all appropriate levels, together with an effective and appropriate diagnostic and treatment and after-care service following evidence-based guidelines;

(h) ensure that due regard is paid to data protection legislation, particularly as it applies to personal health data, prior to implementing cancer screening programmes.

2. Registration and management of screening data

(a) make available centralised data systems needed to run organised screening programmes;

(b) ensure by appropriate means that all persons targeted by the screening programme are invited, by means of a call/recall system, to take part in the programme;

(c) collect, manage and evaluate data on all screening tests, assessment and final diagnoses;

(d) collect, manage and evaluate the data in full accordance with relevant legislation on personal data protection.

3. Monitoring

(a) regularly monitor the process and outcome of organised screening and report these results quickly to the public and the personnel providing the screening;

(b) adhere to the standards defined by the European Network of Cancer Registries in establishing and maintaining the screening databases in full accordance with relevant legislation on personal data protection;

(c) monitor the screening programmes at adequate intervals.

4. Training

adequately train personnel at all levels to ensure that they are able to deliver high quality screening.

5. Compliance

(a) seek a high level of compliance, based on fully informed consent, when organised screening is offered;

(b) take action to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

6. Introduction of novel screening tests taking into account international research results

(a) implement new cancer screening tests in routine healthcare only after they have been evaluated in randomised controlled trials;

(b) run trials, in addition to those on screening-specific parameters and mortality, on subsequent treatment procedures, clinical outcome, side effects, morbidity and quality of life;

(c) assess level of evidence concerning effects of new methods by pooling of trial results from representative settings;

(d) consider the introduction into routine healthcare of potentially promising new screening tests, which are currently being evaluated in randomised controlled trials, once the evidence is conclusive and other relevant aspects, such as cost-effectiveness in the different healthcare systems, have been taken into account;

(e) consider the introduction into routine healthcare of potentially promising new modifications of established screening tests, once the effectiveness of the modification has been successfully evaluated, possibly using other epidemiologically validated surrogate endpoints.

7. Implementation report and follow-up

report to the Commission on the implementation of this Recommendation within three years of its adoption and subsequently at the request of the Commission with a view to contributing to the follow-up of this Recommendation at Community level.

HEREBY INVITES THE COMMISSION:

1. To report on the implementation of cancer screening programmes, on the basis of the information provided by Member States, not later than the end of the fourth year after the date of adoption of this Recommendation, to consider the extent to which the proposed measures are working effectively, and to consider the need for further action.

2. To encourage cooperation between Member States in research and exchange of best practices as regards cancer screening with a view to developing and evaluating new screening methods or improving existing ones.

3. To support European research on cancer screening including the development of new guidelines and the updating of existing guidelines for cancer screening.

Done at Brussels, 2 December 2003.

For the Council
The President
R. MARONI

ANNEX

SCREENING TESTS WHICH FULFIL THE REQUIREMENTS OF THE RECOMMENDATION (*):

— pap smear screening for cervical cancer precursors starting not before the age of 20 and not later than the age of 30;

— mammography screening for breast cancer in women aged 50 to 69 in accordance with European guidelines on quality assurance in mammography;

— faecal occult blood screening for colorectal cancer in men and women aged 50 to 74.

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(*) The indicated age ranges are to be understood as maximum ranges; subject to national epidemiological evidence and prioritisation, smaller age ranges may be appropriate.

Appendix 3

Report from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions

Implementation of the Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC)

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 22.12.2008
COM(2008) 882 final

REPORT FROM THE COMMISSION TO THE COUNCIL, THE EUROPEAN PARLIAMENT, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Implementation of
the Council Recommendation of 2 December 2003 on cancer screening
(2003/878/EC)

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1.   PREFACE

1.1.   **Introduction**

On 2 December 2003 the Health Ministers of the European Union unanimously adopted a Recommendation on cancer screening[1]. The Recommendation on cancer screening of the Council of the European Union acknowledges both the significance of the burden of cancer in the European population and the evidence for effectiveness of breast, cervical and colorectal cancer screening in reducing the burden of disease.

The Council Recommendation spells out fundamental principles of best practice in early detection of cancer and invites Member States to take common action to implement national cancer screening programmes with a population-based approach and with appropriate quality assurance at all levels, taking into account European Quality Assurance Guidelines for Cancer Screening, where they exist. Updated and expanded EU guidelines for breast[2] and cervical[3] cancer screening have recently been published by the Commission; comprehensive European guidelines for quality assurance of colorectal cancer screening are currently in preparation.

The development of new guidelines on cancer screening as a means to foster good health in an ageing Europe, has also been highlighted in the EU Health Strategy[4]. Implementation of the Recommendation has also been supported by the European Parliament through resolutions adopted in 2003[5], 2006[6] and 2008[7].

The Recommendation invites the European Commission to report on the implementation of cancer screening programmes, to consider the extent to which the proposed measures are working effectively, and to consider the need for further action. This is the first such report.

1.2.   **Basis of the report**

In preparing this report, the Commission invited Member States to reply to a written survey in the second half of 2007. 22 of the 27 Member States (82%) returned the questionnaire as of May 2008 (Austria, Belgium, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom).

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[1]   Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC): OJ L327/34-38.
[2]   EU guidelines for quality assurance in breast cancer screening and diagnosis – 4th edition: Luxembourg: Office for Official Publications of the European Communities; ISBN: 92–79–01258–4, catalogue number: ND-73–06–954-EN-C © European Communities, 2006.
[3]   EU guidelines for quality assurance in cervical screening – 2nd edition: Luxembourg: Office for Official Publications of the European Communities; ISBN 978-92-79-07698-5, catalogue number: ND-70-07-117-EN-C © European Communities, 2008.
[4]   Together for Health: A Strategic Approach for the EU 2008-2013, COM(2007) 630 final of 23.10.2007.
[5]   European Parliament resolution of 05 June 2003 on breast cancer in the European Union (P5_TA(2003)0270): OJ C 68 E, 18.3.2004, p. 611.
[6]   European Parliament resolution of 25 October 2006 on breast cancer in the enlarged European Union (P6_TA(2006)0449 B6-0528/2006): OJ C 313 E, 20.12.2006, p.273.
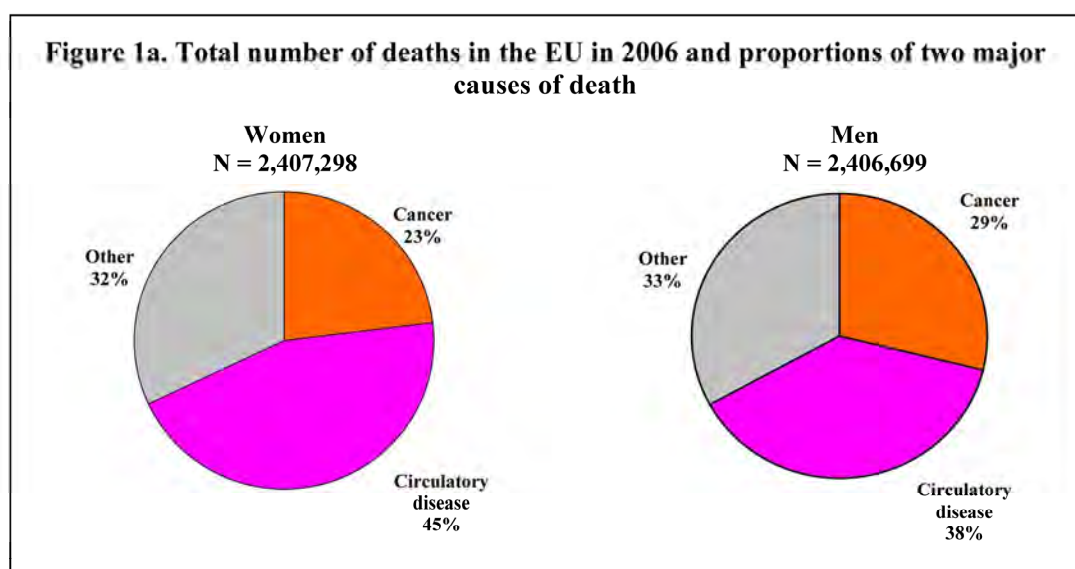[7]   European Parliament resolution of 10 April 2008 on combating cancer in the enlarged European Union (P6_TA(2008)0121).

EN   2   **EN**

This survey was supplemented by information obtained in two ongoing European projects supported by the EU Public Health programme (2003-2008[8]) dealing with monitoring, evaluation and quality assurance of cancer screening: the European Cancer Network (ECN); and the European Network for Information on Cancer (EUNICE).

Population statistics were obtained from the European Statistical System, or from national sources if more recent data was available. Preliminary findings were also discussed with health ministers at the informal health council under the Slovenian Presidency in April 2008, following which several Member States provided further information. This has enabled reporting on programme implementation status for 27 of the 27 Member States. The detailed findings collated and analysed by the European Cancer Network have also been published separately (ECN Report[9]).

1.3.   **The relative burden of cancer as part of the overall burden of disease**

After circulatory disease, cancer is the second most common cause of death in the European Union in 2006, accounting for two out of ten deaths in women, which amounts to a total number of 554,000 women, and three out of ten deaths in men, which amounts to 698,000 men (Figure 1a). Due to the ageing population this number is expected to rise further every year, if no preventive action is taken by the EC and the Member States.

Figure 1a. Total number of deaths in the EU in 2006 and proportions of two major causes of death

Women
N = 2,407,298

Cancer 23%
Other 32%
Circulatory disease 45%

Men
N = 2,406,699

Cancer 29%
Other 33%
Circulatory disease 38%

Source: EUROSTAT 2006

As regards cancer cases, every year, 3.2 million Europeans are diagnosed with cancer, most of whom are suffering from breast, colorectal or lung cancers. But the

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[8]   Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September 2002 adopting a programme of Community action in the field of public health (2003-2008): OJ L271/1-11 of 09.10.2002.

[9]   First report on the implementation of the Council Recommendation on Cancer Screening by the European Cancer Network and the European Network for Information on Cancer: Luxembourg (http://ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf).

EN   3   **EN**

burden of cancer is far from being equally distributed across the European Union (for details see 1.5 below)[10].

As illustrated by national differences in cancer mortality, there is considerable scope to reduce deaths from cancer across the Community by sharing information and exchange of best practice in cancer prevention and control on an EU level. EU cooperation can thus provide significant added value, as developed under "Europe against Cancer" since 1987 for the area of screening for cancer in particular.

1.4. Specific burden of breast, cervical and colorectal cancer

Breast, cervical and colorectal cancer are a major cause of suffering and death in the Member States of the European Union[10]. According to estimates of incidence and mortality by the International Agency for Research on Cancer (IARC), there were 331,000 new cases and 90,000 deaths due to breast cancer, and 36,500 new cases and 15,000 deaths due to cervical cancer[11] among women in the EU in 2006. At the same time new cases of colorectal cancer were estimated at 140,000 in women and 170,000 in men. Colorectal cancer deaths were estimated at 68,000 for women and 78,000 for men in the EU. Together, these cancers account for almost one out of two (47%) new cases and one out of three (32%) cancer deaths in women in the EU. In men, colorectal cancer currently accounts for one out of eight (13%) new cases and one out of nine (11%) cancer deaths (Figures 1b and 1c).

Figure 1b. Total number of cancer cases in the EU in 2006 and proportion of breast, cervical and colorectal cancer[9,10]

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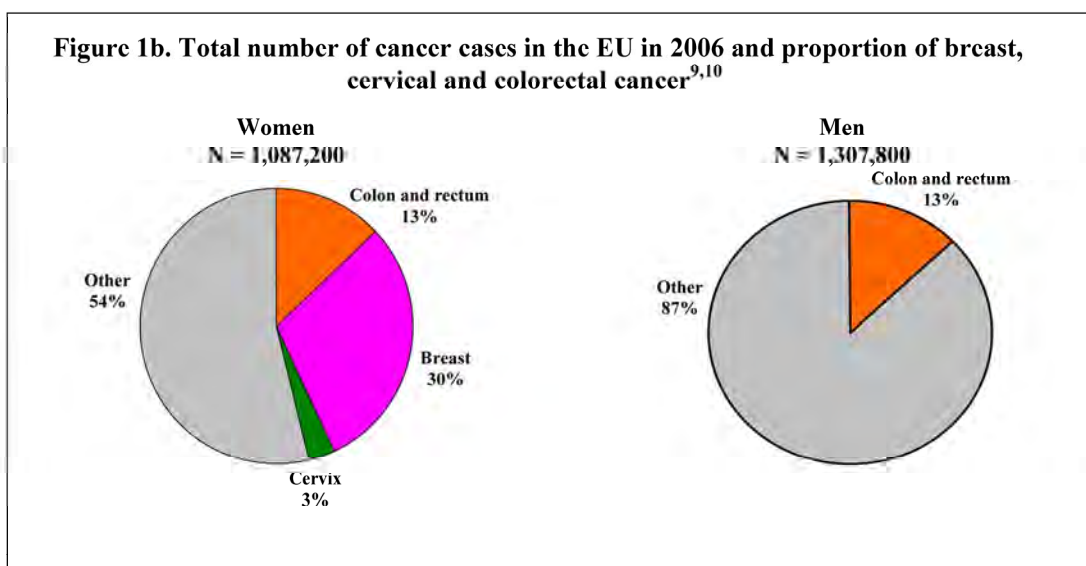
10   Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18: 581-592.

11   IARC mortality estimates for cervical cancer include a proportion of deaths attributed to "unspecified uterine cancer".

Figure 1c. Total number of cancer deaths in the EU in 2006 and proportion of deaths due to breast, cervical and colorectal cancer. Percentages for women do not add up due to rounding[9,10]
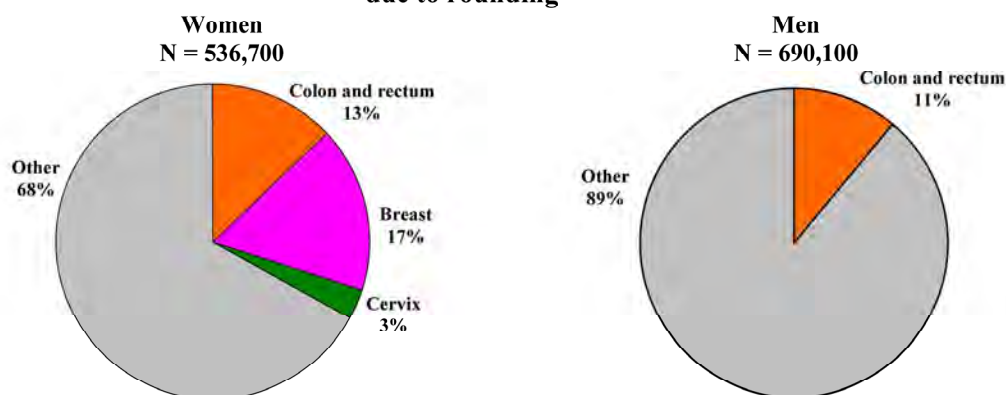
1.5. Diversity of cancer rates in the EU27[11]

Incidence and mortality rates of these cancers vary widely across the EU, reflecting a major health burden in various Member States.

According to IARC estimates the highest incidence rate of breast cancer is 137.8[12] for Belgium, with a mortality rate of 33.5, while the highest mortality rate is 34.5 for Denmark, with an incidence rate of 122.6. The lowest estimated incidence rate for breast cancer is 61.2 for Romania with a mortality rate of 23.9 and the lowest mortality rate is 19.2 for Spain with an incidence rate of 93.6.

The burden of disease is particularly unevenly distributed in the case of cervical cancer. For cervical cancer IARC estimates the highest incidence rate as 24.5 for Romania with the highest mortality rate of 17.0. The lowest incidence rate is 4.9 for Finland and at the same time Finland enjoys the lowest mortality rate of 1.6. The proportion of cancer cases and deaths attributed to this cancer is markedly elevated in all but one of the Member States which acceded to the EU in 2004 and 2007.

For colorectal cancer the highest incidence rate is 106.0 for Hungary, which in addition suffers from the highest mortality rate of 54.4. The lowest incidence rate for colorectal cancer is 31.0 for Greece, which at the same time enjoys the lowest mortality rate of 15.5.

2. RESULTS

2.1. Overview of results

The maps below show the current coverage of population-based screening programmes across the EU.

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[12] Reflecting standard practice, incidence and mortality rates given in this Report are per 100,000 of the population.

Distribution of Breast Cancer Screening Programmes Based on Mammography in the EU in 2007
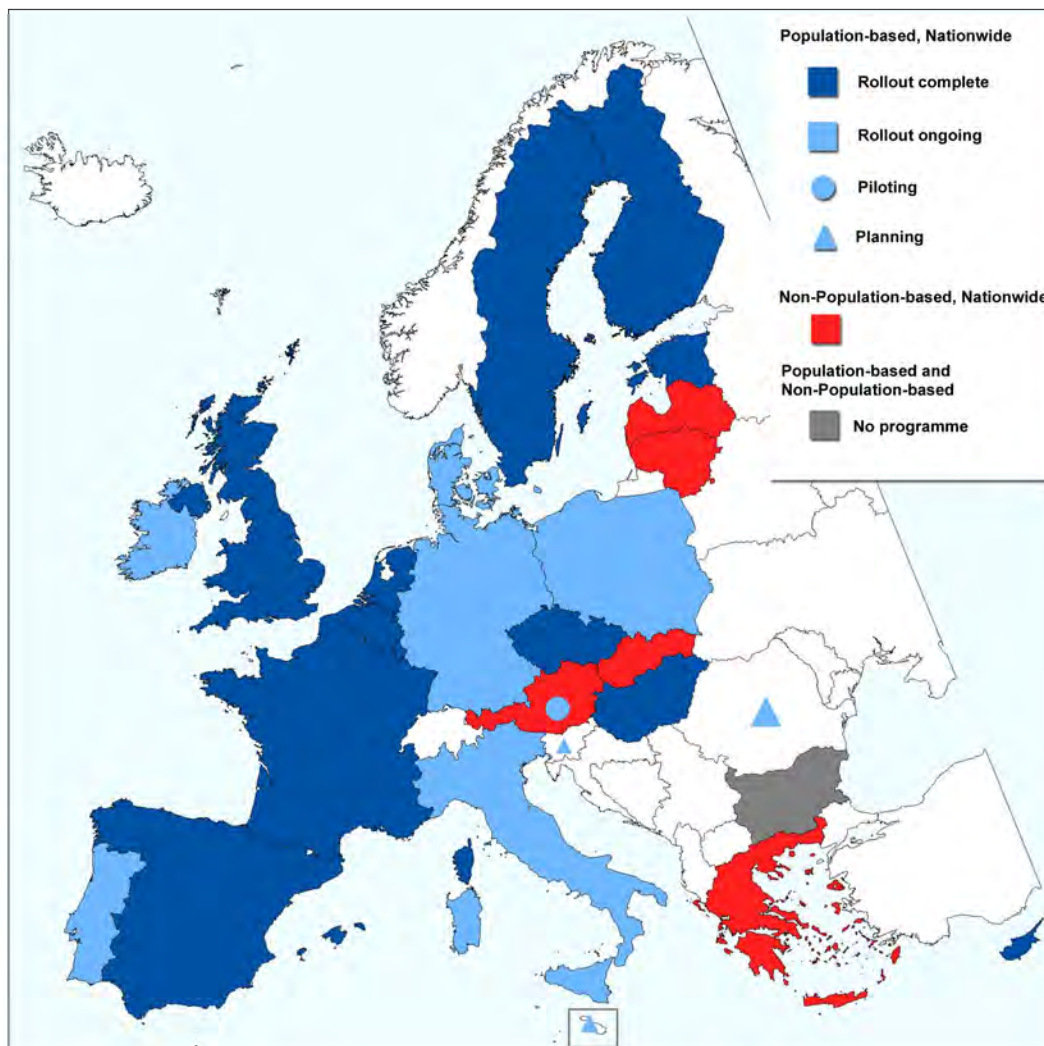
Figure 2. Breast screening programmes in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test (mammography) recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

**Distribution of Cervical Screening Programmes based on Cervical Cytology
in the EU in 2007**

Figure 3. Cervical cancer screening programmes in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test (PAP smear) recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

Distribution of Colorectal Cancer Screening Programmes based on the Faecal occult Blood Test in the EU in 2007
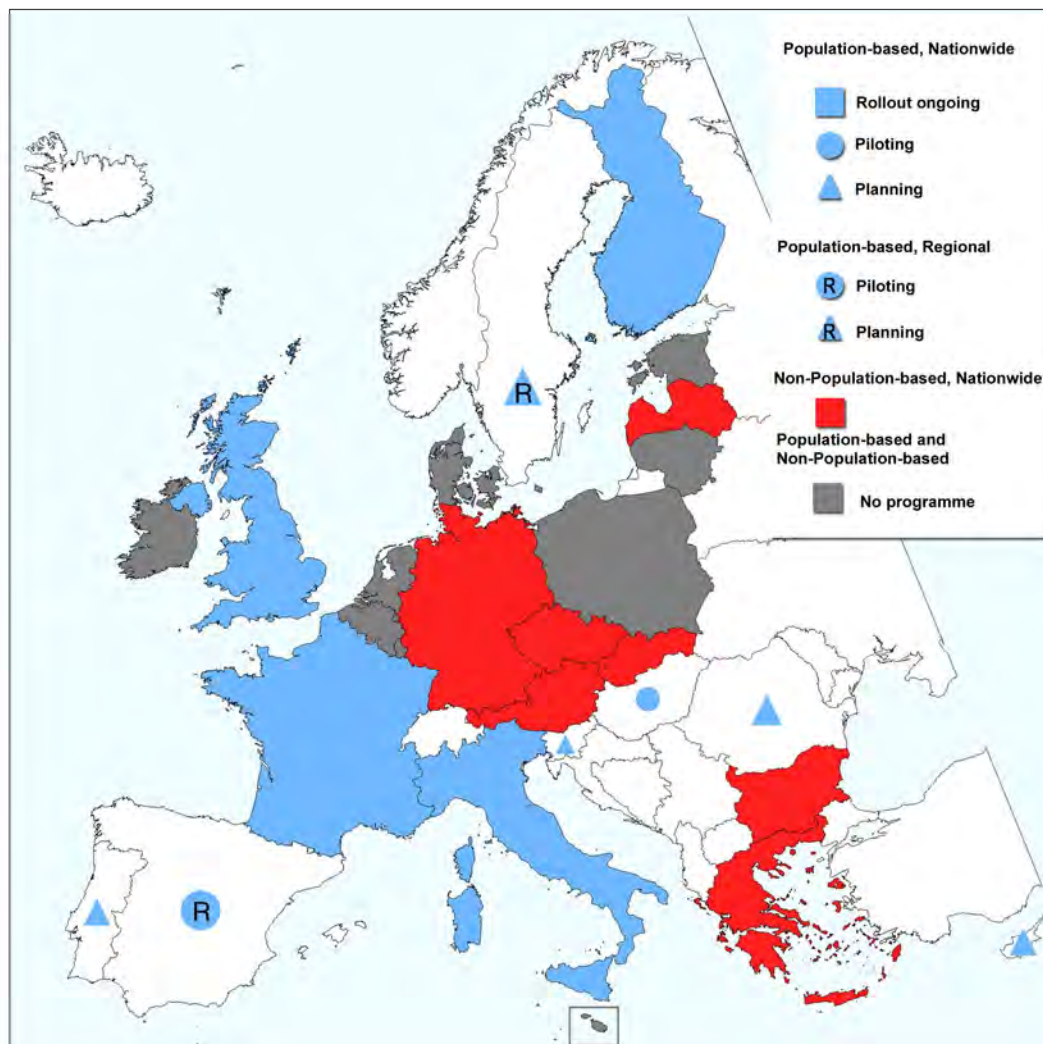
Figure 4. Colorectal cancer screening programmes based on FOBT (faecal occult blood test) in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

As the three maps above indicate, although much progress has been made, more is still required:

- For breast cancer, only 22 Member States are running or establishing population-based screening programmes;

- For cervical cancer, only 15 Member States;

- For colorectal cancer, only 12 Member States.

The current annual volume of screening examinations in the EU is considerable; however, this volume is less than one-half of the minimum annual number of examinations that would be expected if the screening tests specified in the Council Recommendation on cancer screening were available to all EU citizens of appropriate age (approximately 125 million examinations per year). Furthermore, less than one-half of the current volume of examinations (41%) is performed in population-based programmes which provide the organisational framework for implementing comprehensive quality assurance as required by the Council Recommendation.

2.2. Implementation of the Council Recommendation by the Member States

2.2.1. Implementation of cancer screening programmes

Section one of the Council Recommendation comprises a set of safeguards, technical, ethical and legal standards to be followed when implementing screening programmes in the Member States. It covers a set of eight recommendations ensuring a strict evidence base for implementing screening programmes, the recognition of EU guidelines on best practice, the observation of ethical standards in informing on benefits and risks and to be able to adequately follow-up any screen-detected lesion, and last but not least the necessary level of data protection. Most of these eight recommendations, dealing specifically with establishing screening programmes, are reported to be followed by at least two out of three of the Member States (67%).

2.2.2. Registration and management of screening data

Section two comprises a set of four recommendations ensuring the proper functioning of any quality assured screening programme requesting an electronic call/recall system and the collection, management and evaluation of all data from screening tests.

These points are reported to be followed by a very large proportion of the responding Member States. Eighteen out of 22 (82%) use centralized data systems and call/recall systems for running programmes and for inviting all targeted persons, respectively. Twenty out of 22 (91%) Member States report that data is collected, managed and evaluated not just on screening results, but also on assessment of persons with positive screening results and on diagnosis. The same high conformity is reported for data handling in full accordance with European data protection legislation, particularly as it applies to personal health data, prior to implementing cancer screening programmes.

2.2.3. Monitoring

Section three comprises three recommendations aiming to establish the necessary basis for quality insurance by regular monitoring of screening programmes.

Although a majority of the Member States indicate that they comply with two of the three specific items in this section dealing with monitoring screening programmes,

compliance was substantially lower than for most items in all other sections (except section six).

With regard to item 3 (a) in the Council Recommendation, only 55% of the responding Member States report that the process and outcome of organised screening is monitored regularly by an independent peer review and 59% indicate that the results are reported quickly to the general public and to screening staff. The lower proportions of responding Member States performing such monitoring reflect the limited applicability of the respective questions in the EU survey to Member States in which population-based cancer screening programmes have not been initiated. The comparatively very low proportion of Member States which report that national cancer registries monitor screening programmes (45%) will have to be further explored.

2.2.4.   *Training*

Section four contains one recommendation highlighting the importance of training for all health professionals involved in screening programmes.

Very high compliance is reported for section four of the Council Recommendation dealing with training. Twenty out of 22 Member States (91%) report that screening programme personnel is adequately trained at all levels to ensure that they are able to deliver high quality screening.

2.2.5.   *Compliance*

Section five comprises two recommendations seeking high compliance for the population including special action to insure equal access for particular vulnerable social economic population groups.

A high proportion of the Member States indicate that they adhere to these recommendations. Twenty out of 22 Member States (91%) report that a high level of compliance is sought from the eligible population when organised screening is offered. Eighteen out of 22 Member States (82%) report that action is taken to ensure equal access to screening, taking due account of the possible need to target particular socio-economic groups.

2.2.6.   *Introduction of novel screening tests*

Section six comprises a set of five recommendations how to deal with and implement new screening methods for two distinct situations: Novel screening tests and variations or improvements of the recommended screening tests listed in the annex of the Council Recommendation on cancer screening.

Approximately 11 out of the 22 Member States (50%) report adherence to the respective items in section six of the Council Recommendation dealing with introduction of novel screening tests taking into account international research results.

3.   CONCLUSIONS

Four years after the Council of Ministers of the European Union adopted a Recommendation on Cancer Screening, most Member States have acted on the Recommendation and intend to undertake further action where implementation is not yet complete. Thus, the formulation of joint priorities and principles of health policy at the European level has been followed up by actions at the level of the Member States to implement the shared policies and priorities.

Nevertheless, and despite these substantial efforts, overall the EU is still only around half-way towards implementing the Recommendation. Slightly less than half the population who should be covered by screening according to the Recommendation actually are; and less than half of those examinations are performed as part of screening programmes meeting the stipulations of the Recommendation.

This illustrates the need for greater efforts within Member States, supported by collaboration between Member States and professional, organisational and scientific support for Member States seeking to implement or improve population-based screening programmes. Substantial added value may be expected from such support and from additional efforts to improve and maintain high quality of screening programmes.

Work continues to help support the implementation of the Recommendation. For example, development and piloting of EU-wide accreditation/certification schemes[13] for screening services based on EU guidelines for quality assurance of cancer screening would enable programmes to focus efforts on achieving the EU standards. This, in turn, would enable Member States to reap the potential of population-based screening to lower the burden of cancer in the population.

Even though the current volume of activities is still far from the level which can be expected in the future, the current expenditure in human and financial resources is already considerable. A sustained effort is therefore necessary at Community level and within Member States in identifying appropriate and effective measures to assure the quality, effectiveness and cost-effectiveness of current and future screening activities, taking into account scientific developments. Regular, systematic investigation, monitoring, evaluation and EU-wide status reporting on implementation of cancer screening programmes will continue to support exchange of information on successful developments and to identify weak points requiring improvement.

Cancer continues to represent one of the greatest burdens of ill-health within the European Union. The Recommendation on cancer screening represents a shared EU-wide commitment to taking practical steps to minimise that burden in practice, to the benefit of individual citizens and their families as well as to society as a whole. As this Report shows, putting in place these screening measures is a challenging task, and more work is needed to fully implement the Recommendation.

This effort only addresses one aspect of action against cancer. Actions to better monitor and prevent cancer at Community and Member States' level can help to reduce the number of cases arising at all; application of best-practice treatment can help to ensure better outcomes for people with cancer, as can European cooperation on cancer research for the future. The Commission will also consider whether and what further support can be provided to Member States to address other specific issues related to cancer challenges for the future.

In 2009 the Commission intends to launch a partnership for action against cancer. This partnership intends to put in place EU-wide commitments on concrete action to prevent and control cancer and thus contribute to reducing inequalities in tackling cancer. It will aim to support the Member States by providing a framework for

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[13] Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93: OJ L218/30-47 of 13.08.2008.

identifying and sharing information, capacity and expertise in cancer prevention and control, and by engaging relevant stakeholders across the European Union in a collective effort to reduce the burden of ill health that cancer represents.

Appendix 4

List of websites

COUNTRY	WEB SITES
CZECH REPUBLIC	www.kolorektum.cz
DENMARK	www.cancer.dk/international/english/Bowel+cancer+screening.htm
ENGLAND	www.cancerscreening.nhs.uk/bowel/
FINLAND	www.cancer.fi/joukkotarkastusrekisteri/english/
FRANCE InVS InCa	 www.invs.sante.fr/surveillance/cancers/default.htm www.e-cancer.fr/depistage/cancer-colorectal/
GERMANY	www.g-ba.de/institution/themenschwerpunkte/frueherkennung/krebsfrueherkennung/ www.kbv.de/rechtsquellen/2500.html www.zi-berlin.de/cms/projekte/studien/darmkrebs-frueherkennung/
ICELAND	www.krabb.is
IRELAND	www.cancerscreening.ie/colorectal.html
ITALY	www.osservatorionazionalescreening.it www.giscor.it
NORTHERN IRELAND	www.cancerscreening.n-i.nhs.uk
POLAND	www.coi.pl/jelito.htm
PORTUGAL	www.ligacontracancro.pt
SLOVENIA	www.program-svit.si
SPAIN	ppc.cesga.es www.cribadocancer.es (in preparation[*])
SWEDEN	www.swedish.org/Services/Cancer-Institute/Services/Cancer-Prevention-Screening#Colorectal
SWITZERLAND	www.colon-cancer.ch
SCOTLAND	www.nsd.scot.nhs.uk/services/screening/bowelscreening/

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[*] Announced for December 2010

List of tables and figures

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List of abbreviations

ACS	American Cancer Society
AJCC	American Joint Committee on Cancer
AO	Auditable Outcome/s
ASA	American Society of Anaesthesiologists
BMI	Body Mass Index
BSA	Bovine Serum Albumin
CCD	Charge Coupled Device
CE	Conformité Européenne (European conformity)
CEP	Centre for Evidence-based Purchasing
CI	Confidence Interval
CITES	Convention on International Trade in Endangered Species
CJD	Creutzfeldt-Jakob Disease
CMI	Circumferential Margin Involvement
COGS	Conference on Guideline Standardisation
COPD	Chronic Obstructive Pulmonary Disease
CRC	Colorectal Cancer
CRM	Circumferential Margin Involvement
CRT	Chemoradiation Therapy
CS	Colonoscopy
CT	Computerised Tomography
CTC	Computerised Tomography Colonography
DG SANCO	Directorate General for Health and Consumers
DNA	Deoxyribonucleic Acid
DR	Detection Rate
EC	European Commission
EMR	Endoscopic Mucosal Resection
EQAS	External Quality Assessment Scheme
ESD	Endoscopic Submucosal Dissection
ESGE-ESGENA	European Society of Gastrointestinal Endoscopy - European Society of Gastroenterology and Endoscopy Nurses and Associates
EU	European Union
FAP	Familial Adenomatosis Polyposis
FDA	Food and Drug Administration
FICE	Fuji Intelligent Chromo Endoscopy
FIT	Faecal Immunochemical Test

FlexiSig	Flexible Sigmoidoscopy
FOB	Faecal Occult Blood
FOBT	Faecal Occult Blood Test
FS	Flexible Sigmoidoscopy
GCHP	Goblet-cell-rich type of Hyperplastic Polyp
gFOBT	Guaiac Faecal Occult Blood Test
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumour
GP	General Practitioner
Hb	Haemoglobin
HGIEN	High Grade Intraepithelial Neoplasia
HGMN	High Grade Mucosal Neoplasia
HMO	Health Maintenance Organisation
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HP	Hyperplastic Polyp
IARC	International Agency for Research on Cancer
ICRCSN	International Colorectal Cancer Screening Network
ICSN	International Cancer Screening Network
ICT	Information and Communication Technology
IDM	Informed Decision-Making
IEC	International Electrotechnical Commission
iFOBT	Immunochemical Faecal Occult Blood Test
IFU	Instructions For Use
IPDAS	International Patient Decision Aid Standard
IQC	Internal Quality Control
ISO	International Organisation for Standardisation
IT	Information Technology
JP	Juvenile Polyposis
LGMN	Low-Grade Mucosal Neoplasia
LMWH	Low-Molecular-Weight-Heparin
LR	Likelihood Ratio
LST	Laterally Spreading Type
MDT	Multidisciplinary Team
MEI	Magnetic Endoscopic Imaging

MHRA	Medicines and Healthcare products Regulatory Agency
MP	Mixed Polyp
MPHP	Mucin-poor type of Hyperplastic Polyp
MRI	Magnetic Resonance Imaging
MVHP	Microvesicular type of Hyperplastic Polyp
NBI	Narrow Band Imaging
NCCN	National Comprehensive Cancer Network
NHIS	(US) National Health Interview Survey
NHS	National Health Service
NHSBSP	NHS Breast Screening Program
NORCCAP	Norwegian Colorectal Cancer Prevention study
NPS	(US) National Polyp Study
NSAID	Non-Steroidal Anti-Inflammatory Drug
NZHTA	New Zealand Health Technology Assessment
OR	Odds Ratio
PLCO	Prostrate, Lung, Colorectal and Ovarian
PN	Patient Navigation
PNI	Perineural Invasion
PPV	Positive Predictive Value
QA	Quality Assurance
QC	Quality Control
QI	Quality Indicator
QUADAS	Quality Assessment of Diagnosis Accuracy Studies
RCT	Randomised Controlled Trial
RR	Relative Risk
RRR	Relative Risk Reduction
SES	Socioeconomic Status
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SSA	Sessile Serrated Adenoma
SSL	Sessile Serrated Lesion
SSP	Sessile Serrated Polyp
TC	Total Colonoscopy
TEM	Transanal Endoscopic Microsurgery

TNM	Tumour Node Metastasis (classification system)
TSA	Traditional Serrated Adenoma
UICC	Union for International Cancer Control
UKFSS	UK Flexible Sigmoidoscopy Study
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Glossary of terms

Adenoma	A colorectal adenoma is a lesion in the colon or rectum containing unequivocal epithelial neoplasia (see Chapter 7).
Advanced adenoma	In screening programmes the use of the term advanced adenoma has developed and is sometimes used to categorise adenomas for management. In this context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component (see Chapters 3 and 7).
Background incidence rate	The CRC incidence rate expected in the absence of screenng. It is not directly observable but can be estimated.
Cancers	Colorectal cancer diagnosed by the screening programme, or diagnosed as a direct result of participating in the screening programme (see Chapter. 3). Pathologists working in CRC screening programmes define colorectal cancer as adenocarcinoma, i.e. an invasion of neoplastic cells through the muscularis mucosae into the submucosa (see Chapter 7).
Colonoscopy	See *Endoscopic colorectal examination.*
Coverage by examination	Coverage of the screening programme by examination is the extent to which screening examinations have actually been delivered to the eligible population.
Coverage by invitation	Coverage of the screening programme by invitation is the extent to which the invitations sent out by the screening programme within the defined screening interval include the eligible population.
Effectiveness	The reduction in CRC cancer mortality and/or incidence in screening in the target population, under real conditions.
Efficacy	The reduction in CRC mortality and/or incidence in randomised trials; i.e., under ideal conditions. Sometimes used also to describe the effect among those screened.
Eligible population	The eligible population are those people in the target population who fulfil the eligibility criteria specified in the programme policy.
Endoscopic colorectal examination	Endoscopic colorectal examinations visualise the inside of the colon (large intestine and rectum) using flexible optical instruments. Full colonoscopy permits examination of the entire colon. Flexible sigmoidoscopy permits examination of the rectum and the sigmoid colon.
Faecal occult blood test (FOBT)	In vitro stool test which detects hidden blood in stools. The guaiac faecal occult blood test (gFOBT) detects the haem component of haemoglobin, which is identical across

human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract (see Chapter 4).

The immunochemical faecal occult blood test (iFOBT) detects human globin making the test specific for human blood (see Chapter 4).

Fail safe system

System aimed to maximise follow-up compliance or adherence to standard procedures, by sending reminders or applying computer based or other automated checks.

Flexible sigmoidoscopy

See *Endoscopic colorectal examination.*

Follow-up colonoscopy

Included in this group are the participants with a positive screening FS or CS who require a medical appointment for follow-up colonoscopy

Inadequate test

An inadequate FOBT is a test returned by a participant, the results of which cannot be reliably determined (see Chapter 3). The quality is insufficient for processing and the test cannot be used for recording a result according to the programme policy.

The group of participants with an inadequate FS or CS examination are those, the results of which could not be interpreted because of inadequate preparation, and who do not have an adequate screening FS or CS in the reporting period. In such cases a new screening examination should be performed (see Chapter 3).

Interval cancer

A primary CRC cancer, which is diagnosed in a participant who had a screening, test, with/without follow up, which was negative for malignancy, either:
· before the next invitation to screening; or
· within a time period equal to a screening interval for a former participant who has reached the upper age limit for screening.

Invited

The invited are those members of the eligible population who have received an invitation for screening according to the programme policy/process; e.g. invited by mail, by primary care practitioner. NB not all invitations sent may be received.

Lesion

Any abnormality removed or biopsied at endoscopy or surgery.

Opportunistic screening

Screening outside an organised programme, as a result of e.g. a recommendation made during a routine medical consultation, consultation for an unrelated condition, on the basis of a possibly increased risk for developing cervical cancer, or by self-referral.

Organised screening
Screening programmes organised at national or regional level, targeting the whole population at risk and with an explicit policy, a team responsible for organisation of screening and management of screen-positives, including quality assurance and evaluation.

Over-diagnosis with screening
Detection of colorectal cancers or pre-cancerous lesions in screening that might never have progressed to a clinically recognisable cancer during an individual's lifetime.

Participation rate
See *Uptake.*

Positive predictive value (PPV)
The positive predictive value (PPV) for detection of a lesion/ adenoma/ advanced adenoma/ cancer through an FOBT screening programme is defined as the percentage of people with detection of at least one lesion/ adenoma/ advanced adenoma/ cancer at follow-up CS among those with positive tests who have attended follow-up CS.

Positive test
A positive i.e. abnormal FOBT result is a result based on the last adequate test that according to the programme policy leads directly to referral to follow-up colonoscopy.
A positive i.e. abnormal FS or CS screening examination is one resulting either directly in diagnosis of cancer or removal of an adenoma or other lesion, or in referral for further investigation according to the programme policy (see Chapters 2 and 5).

Screened/tested
The group of screened or tested participants are those who have used and returned an FOBT or have attended the FS or CS screening examination irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of tests performed.

Screening episode
The screening test and follow-up based on the test.

Screening interval
Fixed interval between routine screenings decided upon in each programme.

Screening policy
Policy of the screening programme that defines the targeted age group, the geographical area, the screening interval and the screening method.

Sigmoidoscopy
See *Endoscopic colorectal examination.*

Subsequent screening
All screening examinations of individuals within the screening programme following an initial screening examination, regardless of the organisational screening round in which individuals are screened (see Chapters 2 and 3).

Surveillance

Continuous monitoring of disease occurrence within a population. The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage (see Chapter 9).

Target population

The target population are those people of eligible age according to the programme policy residing in the area designated to be served by the screening programme.

Tertiary endoscopy

This group of participants includes those who require an appointment for surgery, or endoscopy performed by a highly qualified expert for removal of challenging lesions following a positive screening FS or CS (or as a consequence of follow-up colonoscopy after primary screening with FS or CS).

Uptake (participation rate)

The number of people who have been screened, within a defined time frame following an invitation, as a proportion of all people who are invited to attend for screening.

Colorectal cancer (CRC) is the most common newly-diagnosed cancer in Europe and the second most common cause of cancer deaths. In the 27 Member States of the EU approximately 330 000 new cases and 150 000 deaths occur each year. Many of these deaths could be avoided through early detection, by making effective use of screening tests followed by appropriate treatment.

In its Recommendation on Cancer Screening of 2 December 2003 the Council of the EU pointed out the need for appropriate quality assurance at all levels when performing CRC screening. That is the aim of the new *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis.*

The multidisciplinary Guidelines are evidence based and build on the positive experience gained from producing the EU Guidelines for breast and cervical cancer screening. They focus on elements essential to screening but also include principles which are equally important in diagnosis such as training, multi-disciplinary teamwork, monitoring and evaluation, cost-effectiveness, minimising adverse effects, and timeliness of further investigations.

The Guidelines include 10 chapters each of which begins with a list of key recommendations. These are graded according to the strength of the recommendation and the supporting evidence. The respective evidence is summarised in the body of the chapters, with explicit citation of over 750 references. In total, more than 250 recommendations are provided.

According to the European Commissioner for Health and Consumer Policy, John Dalli, the new EU Guidelines represent a major achievement with the potential to add substantial value to the efforts of the Member States to improve control of colorectal cancer. Like the previous EU Guidelines for breast and cervical cancer screening, the new EU Guidelines are expected to become an indispensable guide for colorectal cancer screening in the coming years. This, in turn, will save lives and help improve the quality of life of millions of EU citizens, their families and friends.

Publications Office