

Colorectal cancer screening – effect on mortality and incidence rate of colorectal cancer

Report from Norwegian Knowledge Centre for the Health Services No 30 –2008
Overview of documentation and international recommendations

Background: Colorectal cancer (CRC) is the second most common cancer diagnosis in Norway being the third leading cause of cancer-related deaths. The risk of CRC increases with age with 90% of diagnoses occurring in people age 50 years or older. CRC survival rates vary based on the disease stage at the time of diagnosis. CRC is highly treatable in its earlier stages, and appropriate screening may help reduce the incidence and disease burden. Numerous countries, agencies, and health organizations have developed guidelines for screening programs. However, which screening tests to use, which populations and age groups to screen and the frequency of testing are topics that are debated and researched world wide.

The review was requested by the Norwegian Directorate for Health in September 2008 with a timeframe of about four weeks. The aim of this overview is to present summarized results from recent research on the effect of population-based colorectal cancer screening on mortality and incidence of CRC and to evaluate the accuracy of each method. An overview of scree-

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(continued from page one) ning methods recommended in international guidelines for CRC screening programs with focus on average-risk population is provided. **Method:** We searched for systematic reviews, meta-analyses, and other evidence-based literature for CRC screening in Medline, Cochrane Library and HTA databases. We also searched the National Guideline Clearinghouse and National Institute for Clinical Excellence websites for relevant reports and guidelines. We did not search systematically for primary studies. Results from identifies systematic reviews are presented as a narrative syntheses. **Main results:** Repeated CRC screening using FOBT testing annually or biannually followed by colonoscopy for participants with positive test results has shown a reduction in CRC mortality. There is so far no solid evidence on mortality reduction for the other primary screening tests that are available, but this will change with the reporting of findings from ongoing trials. It seems that colorectal screening has no effect on total mortality reduction.

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Executive summary

Background

Colorectal cancer (CRC) is the second most common cancer in Norway and the incidence is increasing for both men and women. The majority of CRCs develops from benign adenomatous polyps through the adenoma-carcinoma stage. CRC may have no detectable symptoms while it is developing and spreading to nearby lymph nodes. The survival is strongly connected with the tumour stadium at the time of diagnosis since early detection and treatment can prevent CRC. This type of cancer is potentially well suited for screening and several screening methods are available. The Norwegian Directorate of Health requested a review (*hasteoppdrag*) of CRC screening in September 2008. The goal was to summarize the evidence on the effect of population-based CRC screening on mortality and incidence of CRC and to evaluate the accuracy of each screening method. An overview of screening methods used internationally was also requested and is also provided in the report.

Method

The following electronic databases were searched for relevant systematic reviews, meta-analyses, HTA reports, and other relevant evidence-based literature on CRC screening: Cochrane Database of Systematic Reviews (CDSR Issue 3 2008), Database of Abstracts of Reviews of Effects (DARE Cochrane Library Issue 4, 2008), HTA (Cochrane Library Issue 4, 2008), and Medline Ovid (1950 to September Week3 2008). The reference lists of retrieved studies were scanned for relevant articles or international guidelines. No systematic search for primary studies was performed. Cost-effectiveness issues were not addressed.

Results

The search resulted in 154 hits. Numerous international guidelines and screening recommendations and other potentially relevant articles and reports were identified through the manual search. A total of 53 articles in full text were reviewed against specified inclusion-exclusion criteria.

The most commonly used CRC screening tests are the Fecal Occult Blood Test (FOBT), flexible sigmoidoscopy, and colonoscopy. A positive test result for FOBT will usually be followed by colonoscopy. The sensitivity and specificity of the FOBT

vary for different brand types (gFOBT and FIT). A systematic review reports the pooled estimate of CRC mortality reduction using the gFOBT as a 16% reduction in the relative risk of CRC mortality as a consequence of annual or biannual screening. There was a 15% relative risk reduction in CRC mortality when only results from biennial screening programs were included. Attendance rates are diminishing over time and the FOBT screening does not seem to affect the incidence of CRC.

The literature identified in this review supports the suitability of flexible sigmoidoscopy and colonoscopy as a screening tool to detect colorectal abnormalities. Endoscopic screening can theoretically prevent development of CRC, but we are still awaiting the evidence from well performed controlled studies. Results from completed randomised trials with sigmoidoscopy will be soon published. A randomized controlled trial with colonoscopy screening is planned (NORDCCAP-II/NordICC).

Other screening methods, such as virtual colonoscopy or DNA stool testing for tumor markers are also under study and the evidence of these methods has not been assessed yet.

Conclusions

Several randomized screening trials have demonstrated a reduction in CRC mortality by repeated FOBT testing annually or biannually followed by colonoscopy for participants with positive test results.

There is so far no solid evidence on CRC mortality reduction for the other primary screening tests that are available, but this will change with the reporting of findings from ongoing trials.

It seems that colorectal screening has no effect on total mortality reduction.

Most of the countries that have implemented CRC screening program use stool tests (gFOBT or FIT) as the primary screening tests followed by colonoscopy for all participants with a positive FOBT.

Oppsummering

Bakgrunn

Kolorektal kreft (CRC) er den nest hyppigst forekommende krefttypen i Norge, og forekomsten er økende både for kvinner og menn. Sykdommen utvikler seg over lang tid via godartede forstadier (adenomatøse polypper) til karsinomer i kolon. Denne utviklingen av CRC er ofte asymptomatisk. Overlevelsen er sterk avhengig av tumorstadiet ved diagnosetidspunktet fordi tidlig oppdagelse og fjerning av adenomer kan forebygge sykdommen. Dette gjør at denne kreftformen er potensielt godt egnet for screening og det finnes flere aktuelle screeningsmetoder.

Nasjonalt kunnskapssenter for helsetjenesten fikk i september 2008 en forespørsel fra Helsedirektoratet om å utføre en oppsummering av evidensgrunnlaget for populasjonsscreening for kolorektalkreft. Hensikten var å vurdere effekt av screening på mortalitet og insidens av kolorektal kreft samt en vurdering av testegenskaper for relevante screeningsmetoder. Helsedirektoratet har også bestilt en oversikt over hvilke tester som anbefales brukt til screening internasjonalt.

Metode

Følgende elektroniske databaser ble søkt i for relevante systematiske oversikter, metaanalyser, HTA rapporter, og annen evidensbasert litteratur om screening av kolorektal kreft: Cochrane Library (Issue 4, 2008): Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), og Medline Ovid (1950 til september, uke3 2008). Vi søkte i referanselister og i websider for andre relevante artikler og internasjonale retningslinjer for screening av kolorektal kreft. Vi gjorde ikke et systematisk søk etter enkeltstudier. Kost-effekt spørsmål er ikke belyst i denne oversikten.

Resultater

Vi fikk 154 treff. I tillegg identifiserte vi flere internasjonale retningslinjer og screeningsanbefalinger samt potensielt relevante artikler og rapporter via håndsøk. Vi vurderte 53 fulltekst artikler i henhold til spesifikke inklusjonskriterier.

Følgende screeningsmetoder for kolorektal kreft er mest brukt: testing av avføring for okkult blod (FOBT), deretter endoskopisk screening med fleksibel sigmoidoskopi (FS) eller koloskopi. Alle individer med positivt FOBT må kolonoskoperes for endelig verifisering av diagnosen. Sensitiviteten og spesifisiteten for FOBT varierer med

merke og testtype (gFOBT eller FIT). FOBT er den eneste screeningsmetoden som har vist effekt på dødelighet av kolorektal kreft i store randomiserte studier. En systematisk oversikt viste en samlet relativ reduksjon på 16 % for dødelighet av kolorektalkreft ved bruk av gFOBT-test som screeningsmetode årlig.

Reduksjon av dødelighet var 15 % i studier med screening hvert annet år. FOBT testen hadde ingen effekt på insidens av kolorektal kreft, og det er rapportert sviktede oppmøte over tid.

Identifisert forskning viser at sigmoidoskopi og koloskopi egner seg til screening for kolorektal kreft. Endoskopisk screening kan teoretisk forebygge kolorektal kreft, men vi venter fortsatt på resultater fra gode kontrollerte studier. Data fra store randomiserte studier fra sigmoidoscopiscreening er underveis.

En randomisert kontrollert studie med koloskopiscreening er under planlegging, med navnet NORDCCAP-II/NordIcc. Det pågår forskning med andre screeningsmetoder som virtuell koloskopi og DNA-markører fra tumor.

Konklusjon

Flere randomiserte screeningstudier har vist en reduksjon i kolorektal dødelighet ved gjentatt FOBT årlig eller annet hvert år og etterfulgt av koloskopi for positive testresultater.

Det er så langt ingen solid dokumentasjon for at andre primære screeningsmetoder reduserer dødelighet av kolorektal kreft, men dette vil forandre seg når rapporteringen fra pågående studier blir tilgjengelig.

Det synes at screening for kolorektal kreft påvirket ikke den totale dødeligheten.

De fleste land som har regionale screeningsprogrammer for kolorektal kreft bruker avføringstest (gFOBT eller FIT) som primær screeningsmetode i kombinasjon med koloskopi.

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Preface

This review was requested by the Norwegian Directorate for Health in September 2008 with a timeframe of about four weeks. The aim of this overview is to present summarized results from recent research on the effect of population-based colorectal cancer (CRC) screening on mortality and incidence of CRC and to evaluate the accuracy of each method. In addition, we were asked to produce an overview of which screening methods are used in other countries.

The intention of this report is to support well-informed decisions in health care that lead to improved quality of the services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

We would like to thank Geir Hoff for sharing his expertise with us in this project.

The Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Oslo, October 2008

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Abbreviations

ACBE	Air Contrast Barium Enema
CRC	Colorectal Cancer
CT	Computed Tomography
CTC	CT (Computed Tomographic) Colonoscopy or CT Colonography (also Virtual Colonoscopy)
DCBE	Double-Contrast Barium Enema
FAP	Familial Adenomatous Polyposis
FIT	Fecal Immunochemical Test (also iFOBT)
FOBT	Fecal Occult Blood Test
FS	Flexible Sigmoidoscopy
gFOBT	Guaiac Fecal Occult Blood Test
HRP	High Risk Polyps
ICRCNS	International Colorectal Cancer Screening Network
iFOBT	Immunochemical Fecal Occult Blood Test (also FIT)
LRP	Low Risk Polyps
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
NORCCAP	Norwegian Colorectal Cancer Prevention Trial
NPV	Negative Predictive Value
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (NCI)
PPV	Positive Predictive Value
RefMan	Reference Manager
RCT	Randomized controlled trial
RR	Relative Risk
SCORE	Once-Only Sigmoidoscopy Trial in Italy
SIGN	Scottish Intercollegiate Guidelines Network
TC	Total Colonoscopy
TNM	Tumor Node Metastasis Classification System
UKFSST	UK Flexible Sigmoidoscopy Screening Trial
USPSTF	US Preventive Services Task Force
WGO	World Gastroenterology Organisation
WHO	World Health Organization

Objective

Colorectal cancer (CRC) is highly treatable and has a high cure rate when it is detected in the earliest stages (1;2) with 5-year survival rates ranging from 5% in the late stages to 90% when it is diagnosed in the earlier stages. Detecting CRC at an early stage is therefore the key issue for screening programmes.

The aim of this review is to summarize the information concerning the effects of various methods for CRC screening. This will be supplemented with information about how and where the methods are implemented.

The following questions are discussed:

- What is the effect of screening for colorectal cancer on the mortality and incidence of colorectal cancer?
- What is the accuracy of the tests/ methods of screening for colorectal cancer?
- To what extent other countries have implemented colorectal cancer screening and which screening methods were chosen?

Background

The term colorectal cancer (CRC) is used to refer to cancers of the colon and rectum. CRC may have no detectable symptoms while it is developing and spreading. By the time an individual has noticeable symptoms of CRC, the cancer may have already reached an advanced stage of disease.

CRC is highly treatable in its earlier stages, and appropriate screening may help reduce the incidence and disease burden of CRC (1-4). The majority of CRCs develop from benign adenomatous polyps through the adenoma-carcinoma sequence of events. This process is slow and therefore favourable in terms of opportunities for intervention and prevention of cancer (5;6). Numerous countries, agencies, and organizations have developed guidelines for screening programs. However, which screening tests to use, which populations and age groups to screen, the frequency of testing, and which healthcare practitioners should be responsible for performing screening tests are topics that are being debated and researched. The cost-effectiveness of various screening tests and screening schedules is also under scrutiny.

This report concerns screening methods for CRC screening and existing guidelines for CRC screening programs. The main focus is average-risk populations. The risks and advantages of the various tests will be discussed briefly. Then, a brief overview of screening guidelines and recommendations in various countries and which screening tests health agencies in those countries are recommending will be provided. Information about a few ongoing clinical trials will also be presented.

EPIDEMIOLOGY OF COLORECTAL CANCER

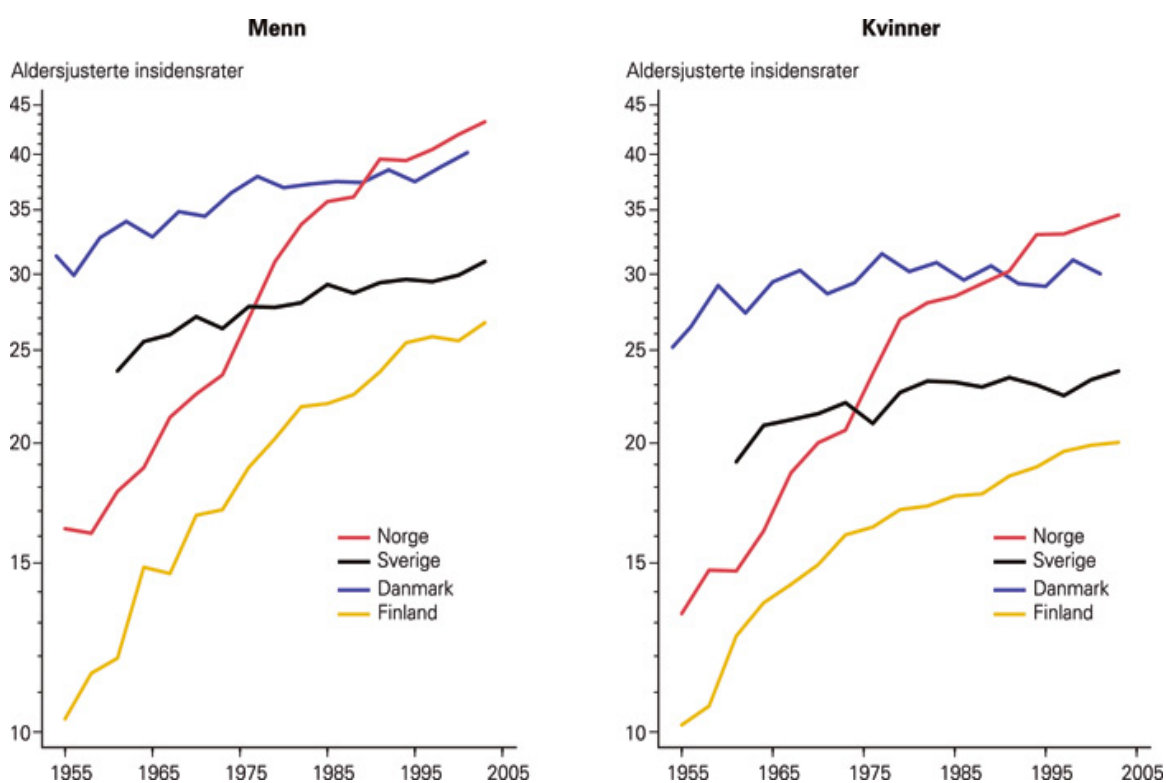
The worldwide incidence of CRC is more than 940,000 a year, and mortality from the disease is almost 500,000 a year (4). CRC is the third most common cancer worldwide (4;7) and the second most common cancer diagnosis in Norway; it is also the third leading cause of cancer-related deaths in Norway. In Norway 3,453 new cases were diagnosed in 2006 (1,686 new cases were men and 1,767 new cases were women) (Figure 1) (8).

The lifetime risk of CRC is approximately 5.9% for men and 5.4% for women. The risk of CRC increases with age (9) with 90% of diagnoses occurring in people older

than 50 (<http://seer.cancer.gov/csr>). The risk of CRC is also associated with some socio-demographic factors and has also been linked to obesity, sedentary lifestyle, and smoking (10). Other known risk factors are inflammatory bowel disease, family history of CRC, and certain genetic mutations, including familial adenomatous polyposis (FAP).

CRC survival rates vary based on the disease stage at the time of diagnosis. The five-year survival rate is around 90% for localized disease (cancer has not spread beyond the bowel wall), 68% for regional disease (i.e. disease with lymph node involvement), and 5-10% for patients with distant metastasis (1;2). The overall 5-year relative survival rate for colon cancer patients in Norway is 58.2% for women and 56.7% for men (1997-2001). The 5-year relative survival rate for rectal¹ cancer patients in Norway is 61.5% for women and 58.7% for men (1997-2001) (8).

Figure 1. Colorectal cancer incidence in Nordic countries (11).



¹ Rectum, rectosigmoid and anus

STAGING OF COLORECTAL CANCER

The staging of CRC uses the same Tumor Node Metastasis (TNM) classification system that is used with other cancer types (12). There are five (0-4) CRC stages (12). CRC may also be staged using the Dukes classification system (13).

Table 1. Colorectal cancer stages

Colorectal cancer stage	Description of different stages
Stage 0	This is the earliest stage possible and is also called <i>carcinoma in situ</i> . “Carcinoma” refers to cancer that starts in epithelial tissue and “in situ” means <i>original position or place</i> . Colorectal cancer is considered stage 0 when it hasn’t moved from where it started; it’s still restricted to the innermost lining of the colon.
Stage 1	In this stage, cancer has extended beyond the innermost layer of the colon into the middle layers of the colon. Stage 1 correlates to Dukes A colorectal cancer.
Stage 2	This correlates to Dukes B colorectal cancer. Colorectal cancer is considered stage 2 after it moves beyond the middle layers of the colon. Sometimes colorectal cancer is still considered stage 2 after it has extended into nearby organs.
Stage 3	If colorectal cancer is found in the lymph nodes, it has reached stage 3 (which correlates to Dukes C colorectal cancer). The subsections (IIIA, IIIB, and IIIC) tell you how many lymph nodes are involved.
Stage 4	Also referred to as Dukes D colorectal cancer, stage 4 is the most advanced colorectal cancer stage. In general, stage 4 colorectal cancer may have spread to nearby lymph nodes and has spread to other parts of the body. Common destinations include the liver and the lungs.

METHODS FOR COLORECTAL CANCER SCREENING

There are several CRC screening tests in use and under development. Different tests may vary in regard to preparatory measures and in their abilities to detect abnormalities; they may also pose different risks to the patient.

Stool tests

Fecal Occult Blood Test (FOBT)

FOBT is a relatively simple test that is widely used (1;14-20). The FOBT involves testing a stool sample for occult, or hidden, blood (21). There are two major types of FOBTs in use: the guaiac FOBT (gFOBT) and the Fecal Immunochemical Test (FIT or iFOBT) (21). Guaiac FOBTs detect the pseudoperoxidase activity of heme in hemoglobin while FITs detect the globin part of the human hemoglobin molecule and

should therefore be more specific in regard to the detection of lower gastrointestinal bleeding (9).

gFOBTs require special dietary restrictions for three to seven days prior to testing; this may include the avoidance of meat, aspirin, some vegetables, Vitamin C, and other foods or medications (9;21). The drying of the sample for the gFOBT may affect the sensitivity of the test; the sample is sometimes rehydrated to increase sensitivity. This technique, however, reduces the specificity of the test (9;10).

FITs do not require dietary modifications prior to the collection of a sample, which may increase patient compliance and adherence as well as reduce the false positive rate (9;10). Numerous commercial solutions are available, and different brands may require different collection and testing procedures.

In general, screening using FOBTs involves collecting and testing more than one sample. A positive result or series of FOBT results requires follow-up examination with another test, such as a flexible sigmoidoscopy or colonoscopy. Studies have found varying rates of sensitivity and specificity for the different types and brands of FOBTs (22).

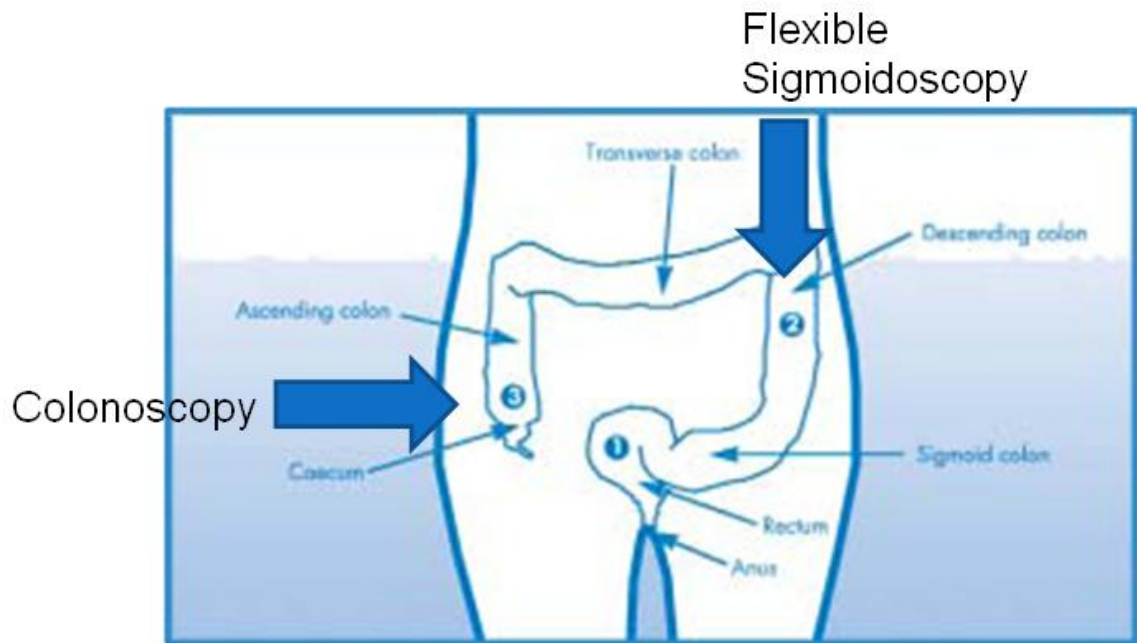
Testing for molecular markers in stool

Molecular markers (genetic (DNA) or epigenetic) stool testing is being studied for its usefulness in identifying CRCs. As the lining of the colon sheds, the cells that are shed appear in the stool. This shedding occurs continuously as opposed to the shedding of blood, which is intermittent. Stool tests for molecular markers try to detect genetic and epigenetic changes in these cells due to the presence of CRC or precancerous polyps. This type of test is still under development (2;23).

Endoscopy

Polyps can be seen and removed during endoscopic examination of the bowel; 90% of adenomas can be seen and removed during colonoscopy and about 70% can be removed during flexible sigmoidoscopy, which is a quicker and generally less difficult procedure and therefore more appropriate for people who are not at especially high risk of CRC (24).

Figure 2. Extent of Flexible Sigmoidoscopy and Colonoscopy Examinations (Image from NICE 2004 - (24))



Flexible Sigmoidoscopy

In a flexible sigmoidoscopy, the rectum and the lower part of the colon, the sigmoid colon, are usually examined using a thin, flexible, lighted tube with about a 1/2 inch diameter called a sigmoidoscope (1). The sigmoidoscope is inserted into the body via the rectum (1). The sigmoidoscope includes a camera lens, so polyps or other abnormal growths, such as tumors, in the rectum or lower part of the colon may be seen during the examination. Due to the limited extent of the examination, abnormalities in the upper part of the colon can not be detected using this test. Mandel (2005) reported that approximately 50% of lesions may be missed by flexible sigmoidoscopy (2).

There are risks associated with sigmoidoscopy, such as perforation or other complications. Prior to the procedure, patients must perform some type of preparation, such as an enema (1) or drinking magnesium citrate, to help clear the bowel. A sedative may or may not be used during the procedure. Several studies have shown that the background, training, and experience of the person performing the sigmoidoscopy or colonoscopy will play a role in the value of sigmoidoscopy or colonoscopy in detecting colorectal disease (1;25;26).

Flexible sigmoidoscopy allows biopsy, which is the removal of tissue samples, and the removal of polyps during the procedure (1). A colonoscopy may be required if abnormalities are detected during the sigmoidoscopy.

Colonoscopy

Colonoscopy allows examination of the entire length of the colon as well as the rectum using a colonoscope, a thin, lighted, flexible tube-shaped scope with a camera lens (1). Colonoscopy may require more extensive bowel preparation than flexible sigmoidoscopy. Patients may need to be on a liquid diet for a day or more prior to the procedure and also drink solutions, such as “oral lavage solutions,” to ensure that the bowel is clean prior to the examination (1). Some form of sedative is often used for the colonoscopy examination, but this practice varies internationally (1;27;28;29). There is a risk of complications, such as bowel perforation, and side effects or other reactions related to the medication used are also possible. In general, serious complications are more common in colonoscopy than in sigmoidoscopy (10).

Colonoscopy ideally allows the visualization of the entire colon and rectum, so polyps and other abnormalities that can not be visualized during the flexible sigmoidoscopy may be seen during a colonoscopy. Polyps may be removed and biopsies taken during the procedure. Some techniques, such as chromoscopy (or dye spraying), are used to increase the ability of colonoscopy to detect colorectal disease or abnormalities (25). As with flexible sigmoidoscopy, the training and experience of the person performing the colonoscopy will play a role in the value of the procedure for detecting colorectal disease. In some countries (UK, USA) nurses have been trained to perform both diagnostic and therapeutic colonoscopies.

Imaging technologies

Imaging technologies such as double-contrast barium enema (DCBE) and CT colonography (virtual colonoscopy), are currently being evaluated as alternatives for CRC screening. DCBE and CT colonography do not allow the healthcare provider to biopsy the bowel or remove polyps during the procedure. Therefore, any polyps or other abnormalities that are detected require further follow-up by flexible sigmoidoscopy or colonoscopy.

Double-contrast barium enema (DCBE)

A double-contrast barium enema (DCBE) (or air contrast barium enema) involves taking x-rays of the entire colon and rectum after the patient has had a barium enema. The barium is drained and then air is injected into the colon (30). X-rays are then taken of the colon and rectum. An instrument called a fluoroscope may also be used to assist in visualizing the colon. Bowel preparation is needed prior to DCBE. Sedation is not needed. It is possible to view abnormalities, such as polyps or cancerous growths, using this procedure. Biopsies and polyp removal are not possible during a DCBE. Therefore, if abnormalities are detected or suspected, further examination, such as a colonoscopy, is needed. A single-contrast barium enema study in which the colon is filled only with a barium enema and not with air and in which larger abnormalities can be identified is also possible (31). Bowel preparation is also

necessary prior to a single-contrast study. Perforation of the bowel may occur during a barium enema examination.

CT colonography (Virtual colonoscopy)

CT (computed tomographic) colonography is a scanning technology that permits a minimally invasive evaluation of the entire colon. During a CT colonography, approximately 2 liters of room air or carbon dioxide are introduced into the colon via a small tube inserted into the rectum. Then, CT scanners are used to generate two- and three-dimensional computer images of the colon (21;26). These images may reveal polyps, cancerous growths, or other abnormalities in the colon. CT colonography can not detect flat lesions. Polyps smaller than 10 mm may not be visualized using virtual colonoscopy (2;21). Sedatives are not required for virtual colonoscopy. However, complete bowel preparation is generally used. Oral barium or iodine contrast can be used to “tag” fecal matter so that it can be “digitally subtracted from the image on the computer” (21;32). Bowel perforation is a risk of CT colonoscopy. It is not possible to remove polyps or perform biopsies during a virtual colonoscopy (32).

The equipment used and the experience and training of the examiner play an important role in how well CT colonography performs as a screening tool. To reduce the risks of exposure to radiation, virtual colonoscopy can also be performed using magnetic resonance imaging (MRI) instead of computed tomography (21;33).

CRITERIA FOR SCREENING ASSESSMENT

In 1968, the World Health Organization proposed principles of screening, which continue to inform screening policy decisions today. The following criteria for screening have been adopted by the WHO and many other countries worldwide (34).

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

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

The natural history of the disease should be adequately understood.

There should be a latent or early symptomatic stage.

There should be a suitable and acceptable screening test or examination.

Facilities for diagnosis and treatment should be available.

There should be an agreed policy on whom to treat as patients.

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

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

Case finding should be a continuing process and not a once and for all project.

Since 1968, modifications of the original principles have been proposed in response to contemporary screening issues and general health care developments. In 1998 the United Kingdom National Screening Committee (UKNSC) developed national criteria for appraising the viability, effectiveness, and appropriateness of a screening program (35). Ideally, all the following criteria should be met before screening for a condition is initiated:

Screening Criteria set by the UK National Screening Committee
(www.nsc.nhs.uk)

The Condition

- The condition should be an important health problem.
- The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
- All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The Test

- There should be a simple, safe, precise and validated screening test.
- The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
- The test should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The Treatment

- There should be an effective treatment or intervention for patients identified through early detection with evidence of early treatment leading to better outcomes than late treatment (nsc/criteria/24/3/03 2).
- There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
- Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The Screening programme

- There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.
- There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

- The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, and treatment)
- The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training, and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money).
- There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
- Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
- Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.
- Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

Method

We conducted this review to support the Norwegian Directorate for Health in updating screening recommendations for CRC screening in the average-risk population.

LITERATURE SEARCH

We initially searched for systematic reviews, meta-analyses, HTA reports, and other evidence-based literature and guidelines for CRC screening. We adapted a search strategy from a recent Cochrane systematic review of stool screening for CRC (36). The scope of this search was expanded to include other methods: flexible sigmoidoscopy and colonoscopy. The search strategy was developed in close cooperation with our librarian (Marit Johansen).

The following electronic databases were searched for relevant studies:

- Cochrane Database of Systematic Reviews (CDSR Issue 3 2008)
- Database of Abstracts of Reviews of Effects (DARE Cochrane Library Issue 4, 2008)
- HTA (Cochrane Library Issue 4, 2008)
- Medline Ovid (1950 to September Week3 2008)

We scanned the reference lists of retrieved studies for relevant articles or international guidelines, and we contacted experts from the field. The literature search was limited to systematic reviews and meta-analyses. We did not search systematically for primary studies. The search strategy is found in Attachment 1.

We did not identify systematic reviews or meta-analyses on the effects of flexible sigmoidoscopy on CRC incidence or mortality. Therefore we decided to report on the results from the randomized controlled trials of sigmoidoscopy that were listed in a recent overview of screening recommendations (4). We did not perform a systematic search for other primary studies of flexible sigmoidoscopy for CRC screening.

To create an overview of screening guidelines and recommendations, we also searched the National Guideline Clearinghouse and National Institute for Clinical Excellence websites for relevant reports.

INCLUSION CRITERIA

Population: men and women age 50 or older from general (unselected) populations.

Intervention: screening methods for colorectal cancer.

Primary methods: FOBT, FIT, flexible sigmoidoscopy, or colonoscopy.

Secondary methods: CT colonoscopy, double-contrast barium enema, or DNA stool testing.

Control: no screening/ usual care or any of the listed screening methods

Outcomes:

Primary: mortality and incidence of CRC

Secondary: accuracy of the method (sensitivity, specificity, positive predictive value, or negative predictive value), harms, and compliance

Other: cost-effectiveness, harms

Languages: Scandinavian languages and English

EXCLUSION CRITERIA

Population: populations with known risk for development of colorectal cancer

Interventions: tests for high-risk population (genetic tests)

SELECTION OF STUDIES

The assessments of all relevant studies were conducted independently by two separate reviewers (KHV, LKJ). Disagreements were discussed in the group until we reached an agreement on whether to include the study. We did not exclude articles on the basis of quality criteria since we did not conduct quality assessments systematically.

DATA EXTRACTION

Data extraction was done independently by the reviewers (KHV, LKH, DJV) with a cross-verification of data by another reviewer.

DATA SYNTHESIS

We reported our findings for each question and for each screening method qualitatively. We did not perform quantitative synthesis for any results.

Results

IDENTIFIED LITERATURE

We identified numerous international guidelines and screening recommendations. We identified 154 abstracts from literature searches and 80 additional potentially relevant articles and reports from reference lists and website searches. A total of 53 articles in full text were reviewed against specified inclusion-exclusion criteria.

Table 2. Search

Database	Date	Hits	Comment
CDSR Issue 3 2008	17.09.08	12	
DARE (Clib) Issue 3 2008	17.09.08	29	
HTA (Clib) Issue 3 2008	17.09.08	38	
Medline Ovid 1950 to September Week 3 2008	25.09.08	90	Ovid's Specificity-filter for reviews
Manual search & website		80	Not a systematic search

We have identified different categories of publications, such as systematic reviews, meta-analyses, guidelines, and even primary studies. We included some primary studies in cases in which they were a supplement to information already summarized in the included systematic reviews. Identified guidelines were mostly used as verification and an update of existing systematic review articles about implementation of CRC screening in different countries. The category and number of publications included are specified in the table (Table 3).

Table 3. Included publication (numbers and category).

HTA re-ports	Systematic reviews and Meta-analysis	Reviews of current practice	Guidelines of current practice	Primary studies
5 HTA re-ports Ref: (10;37-40)	10 SR Ref: (22;36;41-48)	6 reviews Ref: (2;4;49-52)	10 guidelines Ref: (1;3;14;15;20;21;24;53-56)	14 primary studies Ref: (26;57-69)

SUMMARY OF THE INCLUDED SCREENING METHODS

Table 4. Characteristics of CRC screening methods.

Screening Test	Purpose	Considerations	Evidence for recommendations
FOBT (Fecal Occult Blood Test) – Guaiac (gFOBT) – Yearly or Every 2 years	Detects blood (“heme” in hemoglobin) in stool sample.	No bowel preparation needed. Requires dietary and drug restrictions for 3 to 7 days prior to test – avoidance of red meat, some vegetables, Vitamin C, iron, and aspirin. False negative and false positive results are possible. May not detect most polyps and some cancers.	Systematic reviews based on four RCTs with follow-up time up to 18 yrs. (70) Concluding that annual and biennial FOBT reduces mortality rates by 15-16%. Not significant effect on incidence.
FIT or iFOBT (Fecal Immunochemical Test) – yearly or every 2 years	Detects blood (“globin” in hemoglobin) in stool sample.	No bowel preparation needed. No dietary or drug restrictions. False negative and false positive results are possible. May not detect most advanced polyps and some cancers. More specific than Guaiac FOBT (gFOBT) for lower GI bleeding.	No summarized evidence reported on the effect on mortality or incidence. A single RCT with nearly 200,000 participants reported 32% reduction in mortality from rectal cancer (71). Not significant effect on incidence.
Flexible Sigmoidoscopy –Every 5 years	Allows examination of rectum and lower part of the colon. Sometimes allows biopsies.	Requires some bowel preparation. Sedation may or may not be used. Risk of perforation and infection. Does not allow examination of the entire colon so cancers and polyps in the unexamined portion of the colon will be missed.	No summarized evidence. Baseline findings from 4 RCTs on FS screening showed CRC incidence in addition to safety and acceptance.
Combination: FOBT and Flexi-	Increase probability of detect-	See above.	No summarized evidence reported on mortality or

ble Sigmoidoscopy	ing cancers and polyps.		incidence.
Colonoscopy – Every 10 years	Allows examination of rectum and entire colon. Allows biopsies and removal of polyps.	Requires complete bowel preparation. Sedation may or may not be used. Risk of perforation and infection. May not identify all small polyps and cancers.	Lack of RCTs. Metaanalysis of 10 prospective cohort studies indicated that colonoscopy may reduce CRC incidence. Some indirect evidence that screening colonoscopy reduces mortality is published in National Polyp Study(69).
Virtual Colonoscopy (CT Colonography or MRI) –Every 5 years	CT or MRI technology allows computer visualization of entire colon and rectum.	Requires complete bowel preparation. Some risk of perforation. False positive results are possible. May not identify polyps and cancers smaller than 10 mm in diameter. In CT colonography, the patient is exposed to radiation.	No summarized evidence for effectiveness in average-risk population. Several meta-analysis reporting pooled results from randomised studies in high risk population.

EFFECTIVENESS AND ACCURACY OF SCREENING TESTS

Stool testing

We report summarized evidence for the effectiveness and accuracy of FOBT and FIT from four systematic reviews that we identified (1;10;38;70). One review was limited to gFOBT studies (70), but the others included studies with either gFOBT or FIT. The reviews addressed the impact of stool screening tests on CRC mortality and CRC incidence and stage at diagnosis. Only one review reported mortality data for FIT (38). All reviewers reported accuracy of the included stool tests.

Fecal Occult Blood Test (FOBT)

Mortality

Whether screening for CRC using FOBT screening tests reduces mortality due to CRC was addressed in one of the systematic reviews we identified (36). Other benefits, harms, and potential consequences of screening were also included. The review was restricted to trials that utilized repeat invitations to CRC screening. Four randomized controlled trials with more than 327,000 patients were included in the review. The participants were both men and women aged 45- 80 years from the following countries: Denmark (Funen); Sweden (Göteborg); United States (Minnesota); and the United Kingdom (Nottingham). The FOBT (Hemoccult or Hemoccult II) was performed either annually (one trial) or biennially (all four trials). The control group was not invited to attend a screening program. The patients were followed for 11 to 18 years. The number of potential screening rounds ranged from 2 to 11. The non-compliance rates for the trials were from 33% to 46% for the first screening

and from 22% to 40% for at least one round of screening. Mortality analyses were done by intention to treat. Only one out of the four studies included in the review clearly stated that they had included deaths from the complications of treatment for CRC in their CRC mortality analyses (Funen).

Long-term follow-up of biennial FOBT screening indicated that CRC mortality was reduced by between 13% and 21% after 8-13 years of screening in two of the trials while no mortality reduction appeared until after 15 to 18 years of screening in the other two trials (10;38;70). The pooled estimate of CRC mortality reduction in all four FOBT trials at the last follow-up was a 16% reduction in the relative risk of CRC mortality (RR 0.84, 95% CI 0.78-0.90). There was a 15% RR reduction in CRC mortality when only results from biennial screening programmes were included. Compliance with screening varied from 60% to 78% in three trials. When the analyses included only persons who attended at least one round of screening, the results showed a 25% RR reduction (RR 0.75, 95% CI 0.66-0.84).

All-cause mortality

Pooled results showed that there was no difference between intervention and control groups for all-cause mortality (RR 1.00, 95% CI 0.99-1.02) or for all-cause mortality excluding CRC (RR 1.01, 95% CI 1.00-1.03).

FOBT incidence and identified stage of CRC

More early stage CRCs (Dukes A) were detected in the FOBT screening groups in comparison to the control groups, which had more late-stage CRCs (Dukes C or D) across all included trials. Three trials reported the proportion of cancers that were screen-detected to be between 23% and 46% for Dukes A (36). Incidence was unchanged. (70). Table 5 shows the results for mortality reduction and incidence rate of CRC cases in each individual study in the systematic review.

Table 5. Incidence ratio for CRC mortality and mortality reduction in each of the primary studies included in the Cochrane review (36;61)

Strategies for colorectal cancer screening: FOBT or FIT	CRC mortality reduction	Incidence Rate of CRC Cases	
		Screening group (py= person years)	Control group (py= person years)
Minnesota (A)	33% (RR 0.67, 95% CI 0.51-0.83)	32-33/1000	39/1000
Minnesota (B) (18 yr follow-up)	21% (RR 0.79, 95% CI 0.62-0.97)		
Nottingham (B) (11 yr follow-up)	13% (RR 0.87, 95% CI 0.78-0.97)	1.51/ 1000	1,53/1000
Funen (A)	16% (RR 0.84, 95% CI 0.73-0.96)	2,06/1000	2.02/1000

Funen (B) (17 yr follow-up)	11% (RR 0.89, 95% CI 0.78-1.01)		
Göteborg (B) (9 yr follow-up)	16% (RR 0.84, 95% CI 0.71-0.99)	1.53/1000	1,60/1000
Pooled results (36)	16% (RR 0.84, 95% CI 0.78-0.90)	Not reported	Not reported

A=Annual, B=Biennial

FOBT accuracy

The sensitivity of the FOBT (Hemoccult) was defined as the proportion of all CRCs detected during screening (all screen-detected cancers and interval- cancers within 1 or 2 years of screening). Sensitivity varied from 55% to 57% for non-rehydrated slides and from 82% to 92% for the rehydrated slides (36). The positive predictive value (PPV) of the Hemoccult test for CRC in these studies varied from 0.9% to 6.1% (Minnesota) for rehydrated slides and from 5.2% to 18.1% for non-rehydrated slides (36). This means that 80% to 99% of the positive tests were false positives. Reported results from the same systematic review showed low test positivity rate (0.8% to 3.8 %) and higher positive predictive value for CRC (5% to 18.7%) for not rehydrated Hemoccult slides. In comparison, the test positivity rate for rehydrated slides was 1.7% to 15.4 % and the positive predictive value lower at 0.9% to 6.1%.

Attendance

Hewitson et al. reported that the percentage of participants in the screening group who completed at least one round of screening ranged from 60% to 78% (36). Compliance with screening was higher for the Minnesota trial than for the European trials (36).

Fecal immunochemical test (FIT)

Mortality

We identified only one systematic review which included studies of the effectiveness of FITs. The reviewers identified one randomized controlled trial (cluster randomization) with nearly 200,000 participants from China and a follow-up period of 8 years (71). The only statistically significant result was a 32% reduction in CRC mortality (RR, 0.68, 95% CI 0.54 to 0.87) in the screening group compared to the control group. Incidence of CRC was not significantly reduced (RR, 0.98, 95% CI 0.86 to 1.13). (71)

Accuracy

The sensitivity of FIT ranged from 82% to 94% across studies, and the specificity was 87% when testing was performed on patients who were examined by colonoscopy or flexible sigmoidoscopy ((1;10;71). Whitlock et al. reported the results from

several studies in which the sensitivity and specificity of gFOBT and FIT were compared. Significant differences were found between the two test methods (10). Four FIT tests (Magstream/HemeSelect; FlexSureOBT/Hemoccult ICT; OC-Hemodia; Monohaem) had higher sensitivity (61% to 91%) for CRC than estimates for nonrehydrated Hemoccult II (25 to 38%) (10).

Attendance

The participation rate in the study was 66% (one-off screen). All FIT-positive participants underwent flexible sigmoidoscopy (71).

Complications of FOBT or FIT

Evidence about the harms or negative effects of fecal tests is lacking. There is no direct harm connected to the method, but the relatively high proportion of false positives may cause further unnecessary investigations, which might be harmful. Also, there is possible harm from the psychological stress and uncertainty that might be associated with a positive test result.

Endoscopy

Flexible Sigmoidoscopy (FS)

Two systematic review on FS was found, one was excluded because it did not report on the incidence or mortality of CRC (44). We used the recent health technology assessments report from the US Agency for Healthcare Research and Quality (ARHQ) for outcomes on the accuracy and complication rates for screening with FS (10). For mortality and incidence outcomes we decided to describe the baseline results from large primary studies on FS screening as reported in a review aimed at identifying recent screening initiatives (4).

Four large-scale, community-based randomized clinical trials are underway that evaluate FS as a screening tool. Initial results have been published from these trials, but follow-up data (e.g. mortality data) have not yet been published. All four studies are large multi-center studies, one from Norway (NORCCAP)² (59), one from the UK (UKFSST)³ (57), one from Italy (SCORE)⁴ (64), and one from the USA (PLCO)⁵ (68). The European studies integrate biopsy into the sigmoidoscopy screening procedure and conduct colonoscopy according to prespecified criteria while the American PLCO study does not. The Norwegian study NORCCAP (59) includes a comparison between once-only FS and FS plus FOBT. The PLCO study is evaluating the effectiveness of repeated cancer screening tests (including FS screening every 3-5 years) on site-specific cancer mortality while the three other studies are offering

² Norwegian Colorectal Cancer Prevention Trial

³ UK Flexible Sigmoidoscopy screening Trial

⁴ Once-only Sigmoidoscopy Trial in Italy

⁵ Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

one-time FS screening. All four are well-designed studies and are expected to provide reliable evidence concerning health outcomes following FS screening (Table 6).

Table 6: Characteristics of Flexible Sigmoidoscopy trials

Sigmoidoscopy trials	No. assigned to screened group (no. screened) & Ages screened	% with detected CRC Stage Adenoma	Complications (perforations, bleeding)
UKFSST (57) UK (14 centers)	57 254 (40 674) 55-64 yrs	0.34% of those screened, Dukes stage A and Dukes stage B findings: 74% Adenoma (distal): 12%	1 perforation (4 perforations after colonoscopy follow-up) 12 bleeding incidents
PLCO (68) USA (10 centers)	77 465 (64 658) 55-74 yrs	0.29% of those screened, Stage I and Stage II findings : 77% Adenoma (distal): 7.2%	N/A
SCORE (64) Italy (6 centers)	17 148 (9 911) 55-64 yrs	0.54% of those screened, Dukes stage A findings: 54% Adenoma (distal): 10.8%	1 perforation (1 perforation after colonoscopy follow up) 1 hemorrhage
NORCCAP (59) ^a Norway (Oslo/Telemark)	20 003 (12 960) 50-64yrs	0.32% of those screened, Dukes stage A and Dukes stage B findings:N/A Adenoma (any): 17%	No serious complications, 0.2% minor complications (mostly vasovagal reactions)

^a NORCCAP compared once-only FS in one half of the intervention and FS plus FOBT testing in the other half of the intervention. N/A not available

CRC mortality

No large-scale RCTs have been completed that provide data on the impact of FS-screening on mortality. In two case-control studies, flexible sigmoidoscopy was associated with a 60-80% reduction in CRC mortality for the area of the colon within its reach, and this protective effect appeared to persist for 10 years (62;72).

Three of the ongoing trials are expected to report mortality data later this year, at the earliest. The PLCO trial will not report mortality data until 2010-2012 (68).

Incidence and identification of stages of CRC

Cancer and adenoma yields varied across studies (Table 6). We have not pooled data across the studies. The results from each study are summarized in Table 6.

Cancer yields were relative high in Italy, 0.54%, while in other trials the cancer yield was between 0.29% and 0.34%. Most of the cancers were Stage I and II (Dukes A and B). For adenomas, yields were relative high in Norway (17%, including all adenomas) compared to the other trials where adenoma yields were lower than in the Norwegian study (between 7.2% and 12%, including distal adenomas).

One small randomized clinical trial of FS screening in Oslo/Telemark (TPS-1; Telemark Polyp studie – 1) reported an 80% reduction in CRC incidence rates with a 13-year follow-up (67). However, the number of patients and CRC events in this study is were small. More information on CRC incidence will appear when the results from the four RCTs become available (Table 6). In one study the detection of advanced neoplasia by FS alone was about 70%, but the detection rate increased to 76% with the addition of FOBT due to the identification of proximal lesions (73).

Accuracy of FS

According to the recent HTA report from AHRQ, the estimated sensitivity of flexible sigmoidoscopy, with and without biopsy, for advanced neoplasia throughout the colon ranges from 72% to 86% with possibly lower (but less precise) estimates for CRC throughout the whole colon (58% to 75%) (10). The imperfect sensitivity of flexible sigmoidoscopy is recognized and may be the result of many factors, including limited examination of the colon, variable performance by examiners, lack of standardized protocols for colonoscopic referral, and differing risks for advanced proximal neoplasia among patients (10). Studies comparing flexible sigmoidoscopy to colonoscopy have found that the shorter exam is 60% to 70% sensitive for CRC and advanced adenomas in comparison to the complete exam, colonoscopy. The sensitivity of FS in detecting advanced neoplasia is reported to be 35-70% by a recent guideline (20). This screening method does, however, miss some proximal lesions in individuals who have no index distal lesions to warrant colonoscopy. Results vary according to several factors, including gender and ethnicity (49). Determining whether the sensitivity of FS protocols differs is an important issue. When the results from the ongoing trials become available, it will be important to review this issue (10).

Complications of FS screening

Baseline and procedural data from all four trials suggest that screening with flexible sigmoidoscopy is safe (no major complications and relatively few perforations) (57;59;63;64;68).

The recently published HTA from AHRQ (10) reported on harm from FS. Serious complications from FS in average-risk populations (pooling of 6 studies, n=126,985) is 3.4 per 10,000 procedures (95 percent CI 0.61 to 19 per 10,000 procedures), and are much less common than in colonoscopy (10). Serious complications include perforation, hemorrhage, diverticulitis, cardiovascular events, severe abdominal pain, and death (10).

Attendance

Participants' attendance rate differs between the FS studies. The Italian SCORE study had the lowest compliance with 58% and the US study PLCO had the highest compliance with 83%.

Total colonoscopy

There have been no large population-based RCTs examining the effectiveness of colonoscopy in reducing mortality from CRC when colonoscopy is used as the primary screening tool for this disease (1;10). We identified one HTA report and one systematic review in our search on primary screening of CRC with colonoscopy (10;47). ARHQ's HTA reported on the accuracy and complication rates of screening with TS (10). Niv et al (47) reported on incidence and complication rates.

Niv et al (47) performed a meta-analysis of 10 prospective cohort studies using colonoscopy for screening average-risk populations for CRC; these studies had a total of 68,324 patients. A weakness of this study is that at least 4 of the included studies had heterogenous populations including both high- and average-risk participants. A separate calculation on only average-risk participants was not performed because the data were uniformly presented in the primary studies (47). Five of the studies were from the USA, one was from Taiwan, and one was done in both the USA and Taiwan. Other studies were from Spain, Israel, and Poland. The number of participants varied from 627 to 50,148 (47). The pooled results from the meta-analysis are presented in Table 7.

Table 7. Meta-analysis of prospective cohort studies using total colonoscopy for screening CRC (47).

Strategies for colorectal cancer screening	Detection of Colorectal cancer	Complications – perforations and bleedings
Colonoscopy (pooled analysis of 10 studies) (47)	0.78% (CI 0.13-2.97%)	Perforations: 0.01% (CI 0.006-0.02%)
	Stage I and Stage II findings: 77%	Bleeding incidents: 0.05% (CI 0.02-0.09%)
	Advanced adenoma: 5% (CI 4-6%)	

CRC mortality

We found no reliable data on the effect of colonoscopy screening on mortality.

Accuracy of total colonoscopy

Colonoscopy is generally considered the reference standard for investigation of the large bowel and holds an established place in the diagnosis and treatment of CRC.

The meta-analysis from Niv et al. (47) did not report on the accuracy of total colonoscopy.

Incidence and identification of stages of CRC

CRC was found in 0.78% of the participants (47). Stage I and II together were found in 77% of the cancers diagnosed. At least one adenoma was found in 19% of patients (95% CI 15-23%) and advanced adenoma in 5% (95% CI 4-6%). For further information on incidence, the National Polyp Study reported a reduction in the incidence of CRC when comparing those who had a complete colonoscopy where all adenomas were removed to 3 reference groups. The reference groups were patients with polyps \geq 1 cm who declined to undergo surgery, patients who had all rectal adenomas removed, and, as the final cohort, a sample of the general population (69).

Complications of colonoscopy screening

Complications were rare and are described as pooled results for the 10 cohorts (Table 6). The perforation rate was 1:10,000 and the bleeding rate was 1:2,000 (for CI, see Table 6). The newly published HTA from AHRQ (10) reported on harm from colonoscopy. Serious complications from colonoscopy in average-risk populations (pooling of 11 studies, n=55,211) occurred at a rate of 3.1 per 1,000 procedures (95% CI of 1.68 to 5.76) (10). These data regarding serious complications included studies in which colonoscopy was used as a diagnostic method following by FOBT or FS as the primary screening test, and therefore the direct relevance to colonoscopy as a screening method is limited (10). Serious complications included perforation, hemorrhage, diverticulitis, cardiovascular events, severe abdominal pain, and death (10).

Chromoscopy

Four RCTs including 1009 patients were summarized in a Cochrane review comparing colonoscopy with chromoscopy to regular colonoscopy (25). The trials in this systematic review included participants in screening programmes for surveillance. Chromoscopy was likely to yield significantly more patients with at least one neoplastic lesion (OR 1.61 (95% CI 1.24-2.09)) and significantly more patients with three or more neoplastic lesions (OR 2.55 (95% CI 1.49-4.35)) (25).

CT colonography

In some clinical guidelines it is recommended that CT colonoscopy (CTC) may be used as an alternative to diagnostic colonoscopy. We identified four meta-analyses performed with prospective controlled studies assessing the value of CT colonoscopy as an alternative to colonoscopy. All identified meta-analyses included studies with either asymptomatic or symptomatic high-risk patients or patients with a positive FOBT test. No systematic reviews or meta-analyses on the use of CTC as a screening method in an average-risk population were identified. Because CTC is included as a part of screening programs in some countries, we have briefly described results from

recently published systematic reviews and meta-analyses to illustrate the accuracy of this method (42;43;48).

Mortality

There were no published results from randomized controlled clinical trials to directly establish the effectiveness of virtual colonoscopy in decreasing CRC mortality (1).

Accuracy

The sensitivity and specificity of the findings are dependent on the size of polyps. A systematic review by Walleser et al. (2007) assessed the value of CT colonoscopy as an alternative to regular colonoscopy in FOBT-positive individuals (74) for the detection of lesions 10 mm or greater and cancers in non- screening populations. The authors reported a pooled sensitivity of 63% (95% CI 0.55 to 0.71) and specificity of 95% (95% CI 0.94 to 0.97) for lesions 10 mm or greater. Sensitivity for CRC was 89% (95% CI 0.70 to 0.98) with specificity of 97% (95% CI, 0.95 to 0.98). The corresponding values for regular colonoscopy were 95% sensitivity (95% CI 0.90 to 0.98) and 99.8% specificity (95% CI 0.99-1.00) for lesions 10 mm or greater and 96% sensitivity (95% CI 0.80 to 1.00) and 99.7% specificity (95% CI 0.99 to 1.00) for CRC.

Other identified meta-analyses reported pooled results from studies with symptomatic patients or patients with a history of colorectal neoplasia or a positive screening test (46;42). One meta-analysis reported a sensitivity of 85% for polyps >9 mm and 48% for polyps < 6 mm while another reported a sensitivity of 82% for polyps larger than 10 mm and 56% for polyps up to 5 mm (46;42) .

One recent study evaluated the sensitivity of CT colonography in the identification of adenomas or cancers at least 10 mm in diameter detected by colonoscopy in asymptomatic adults (2600 participants). 89% of the participants had no CRC risk factors other than age. CT colonography detection of adenomas and adenocarcinomas had a sensitivity of 90%, a specificity of 86%, a positive predictive value (PPV) of 23%, and a negative predictive value (NPV) of 99% for lesions 10 mm or more in size (60).

Complications

There is a small risk of bowel perforation during CT colonography. Also, patients are exposed to radiation (21;75).

IMPACT OF SCREENING ON CRC MORTALITY

The impact of CRC screening on mortality reduction was reported only for gFOBT screening using Hemoccult II. Longer-term follow-up for gFOBT screening trials indicates a 16 % mortality reduction. There are no screening trials reporting mortal-

ity outcomes for any other relevant methods. We have described below the results for mortality reduction for relevant CRC screening methods which were reported in included systematic reviews.

Table 8: Reduction in CRC mortality and all-cause mortality

Screening test	Reduction in CRC mortality	Reduction in all-cause mortality	Evidence
gFOBT	16%	No difference	Pooled results from four RCT trials (10;70).
FIT	32% <i>No pooled results</i>	No published results	No summarized evidence or evidence from RCTs. Large cohort study reported in one SR (10;71) indicated 32% CRC mortality reduction.
Flexible sigmoidoscopy	60-80% <i>No pooled results</i>	No published results	No summarized evidence or evidence from large RCTs. Two case-control studies reported 60-80% reduction in colorectal cancer mortality for the area of the colon within its reach (62;72).
Colonoscopy	No published results	No published results	No summarized evidence or evidence from large RCTs. (1;10)
CT colonography	No published results	No published results	No summarized evidence or evidence from large RCTs. (1;10)

At the time of this report, results from a number of trials or studies of CRC screening methods are pending (See Ongoing studies table in Appendix 3). Those studies include four trials of FS addressing mortality reduction; one is a Norwegian study (NORCCAP) (10).

ACCURACY OF SCREENING METHODS FOR CRC

The accuracy of screening methods for CRC varies. Table 9 presents an overview of the overall reported accuracy (58) .

Table 9: Accuracy of methods for colorectal screening compared with colonoscopy (58;74)

Screening test	Sensitivity (Polyps)	Sensitivity (CRC)	Specificity
gFOBT (unrehydrated)	10% (5- 20) (LRP+HRP)	33%(20-40)	97% (95-99)
Sigmoidoscopy	85% (80-85) (LRP)	95% (85-90) (HRP + CRC)	100%*
Double-contrast barium enema	30% (30-50) (LRP) 50% (50-70) (HRP)	70%(60-90)	86% (80-98)
CT colono- scopy		89% (70-98)	97% (95-98) 95% (94-97)
	63% (55-71) Polyps > 10mm		

*Only valid for lower part of colon

LRP= Low Risk polyps; HRP= High Risk polyps

ATTENDANCE RATE AND DETECTION RATE

For all screening modalities, the effectiveness decreases substantially as adherence to the regimen declines. At the individual level, adherence to the screening regimen will be more important in life-years gained than will the particular regimen selected.

We identified one RCT comparing attendance and detection rates of colonoscopy with FS and FIT. The study was done in Italy (SCORE3) (66). The participation rate was about 30% for all methods with the lowest rate for total colonoscopy (27%). The detection rate of advanced neoplasia was highest using colonoscopy.

See the results presented below (Table 10).

Table 10: Attendance and detection rates, from the SCORE3-study (66).

Strategies for colorectal cancer screening	Attendance rate	Detection of Colorectal cancer	Detection of advanced adenomas	Number needed to screen to detect 1 advanced adenoma
FIT	32.3% (1965/6075)	2 (0.1%)	21 (1.1%)	264
Sigmoidoscopy	32.3% (1944/6018)	12 (0.6%)	86 (4.5%)	60
Colonoscopy	26.5% (1597/6021)	13 (0.8%)	100 (6.3%)	53

Current data are insufficient to predict adherence to any specific screening program at the population level, but reported adherence from the trials is an important guide to say something about expectations (10).

RECOMMENDED SCREENING METHODS

We identified three recent overview articles (4;39;51) that examined recent and on-going policies and screening initiatives. There is no consensus on screening recommendations, and many countries have not yet implemented nationwide screening or the screening programs only exist on the pilot, research, or local level. In North America and Europe as well as in Australia and New Zealand, there is a widespread scientific agreement on the value of CRC screening. CRC screening is endorsed by the American Cancer Society, the US Preventive Services Task Force (USPSTF), the Multi-Society Taskforce on Colorectal Cancer, the American Gastroenterological Association, the American College of Physicians, the British Society of Gastroenterology, the Canadian Taskforce on Preventive Health Care, and the Royal Colleges of Physicians in the UK (20).

A review by Gutierrez-Ibarluzea et al. summarized CRC screening recommendations in Europe for average-risk individuals at the population level (39). Within the United States, different agencies, organizations, and medical communities present different screening recommendations (53;76;77). The US Agency for Healthcare Research and Quality (AHRQ) recently reviewed the scientific literature on CRC screening. They recommend screening between the age of 50 and 75 years using either FOBT, sigmoidoscopy, or colonoscopy as the primary test with various screening intervals depending on the type of test (10; 82). Virtual colonoscopy and DCBE is also in use (1). The USPSTF concluded that, for adults, age 76 to 85 years, there is moderate certainty that the net benefits of screening are small while for adults over age 85 the benefits of CRC screening do not outweigh the harms. The Canadian Task Force on Preventive Health Care recommends both FOBT and FS in periodic health examinations of asymptomatic people over 50 years of age (<http://www.cmaj.ca>). Australia

has a national guideline. In Asia, national guidelines are available only in Japan, Korea, Taiwan, and Singapore (20). Some Asian countries (Japan and soon Taiwan) have started using immunochemical FOBT (FIT) as a screening test.

The European Union recommends the use of annual or biennial FOBTs as a screening tool for people 50 to 74 years of age; positive FOBT results are to be followed by a colonoscopy (14;15). Germany, Austria, France, and the United Kingdom have national screening programs that include FOBT yearly (Germany and Austria) or every 2 years (France and the UK). Some countries, such as Germany, recommend colonoscopy at an interval of every 10 years for additional screening while others, such as Austria, use a combination of sigmoidoscopy every 5 years and colonoscopy every 10 years. The Finnish authorities decided to introduce a CRC screening program in the form of a randomized trial (gFOBT vs. no screening). The implementation of CRC screening in Finland, which is measured by attendance and the performance of the gFOBT, has been considered a success, but the mortality effect is expected to appear only after several years (16).

For an overview of international recommendations for CRC screening, see the tables below. (Tables 11-13)(4;39;51).

Table 11 . Comparison among countries with population screening programs at the national level in Europe -Screening Characteristics (4;39;51).

Country	Germany	Austria	France	England, Northern Ireland and Wales	Czech republic	Italy *	Poland
Periodicity	Yearly (recommended) and 10 years	Yearly (recommended) , 5 years, and 10 years	Every 2 years	Every 2 years	Every 2 years	Every 2 years	Every 10 years
Ages Screened	>50 years	>50 years	50-74 years	60-69 years	>50 years	50-70 years	50-65 years
Technique(s) Used	FOBT (annual) Colonoscopy (10 years)	FOBT (annual) Sigmoidoscopy (5 years) Colonoscopy (10 years)	FOBT (un-rehydrated)	FOBT (un-rehydrated)	FOBT	FOBT (FS)*	Colonoscopy
Other Screenings	Yes	Yes	Yes	No	N/A	N/A	N/A
Population	82,310,000	8,206,524	63,213,894	55,045,085	3,700,000 ¹	N/A	6,500,000 ¹
Comments						* 4 programs One is FS	

¹Target population in age range

Table 12. Comparison among countries with population screening guidelines and recommendations at the national level outside Europe - Screening Characteristics (4;39;51).

Country	USA	Canada	Japan	Israel
Periodicity	Yearly , 5 years, and 10 years	Every 5 years	Every 2 years	Yearly
Ages Screened	>50 years	>50 years	>40 years	50-74 years
Technique Used	FOBT (annual) Sigmoidoscopy (5 years) Colonoscopy (10 years)	FS	FOBT	iFOBT (Immunological)
Other Screenings	N/A	N/A	N/A	N/A
Population	500,000 ¹	500,000 ¹	35,000,000 ¹	700,000 ¹
Comments	National screening guidelines	No polyp removal		

¹Target population in age range

Table 13. Research activities in different countries (4;39;51).

Screening test	FOBT	Sigmoidoscopy (FS)	Total colonoscopy
Countries	Sweden, Taiwan, Finland, France, Denmark, The Netherlands, Italy, Spain, Switzerland, UK, Canada, USA, Australia, Taiwan; New Zealand	UK, UK (nurse-led), Norway, The Netherlands, Italy, Belgium, Switzerland, USA, Canada, Australia; New Zealand	USA, Italy, Switzerland, Hong Kong,

Screening is available in different settings, but the vast majority of screening activities are still opportunistic and uncoordinated. In certain localities, large health care systems have developed organized screening for their populations. In a recent survey conducted by the International Digestive Cancer Alliance (IDCA) across Europe, 21 out of 39 nations have reported national screening guidelines promoted by medical and professional organizations. (20;52). There are numerous CRC screening trials going on at the local or regional level with FOBT, sigmoidoscopy, or colonoscopy. We have made a list of ongoing clinical trials which have completed the inclusion of participants. See attachment (2).

Discussion

This review provides an overview of the evidence for the effectiveness of different methods for CRC screening. Due to the rapid need for information on this topic, we have only assessed existing systematic reviews and a selection of single studies. Therefore, we may have missed relevant documentation, particularly studies that may have been published recently.

Our main focus was on the effectiveness of different screening methods for CRC. We have not focused on possible negative effects of such screening programs or addressed cost-effectiveness issues.

Does screening reduce mortality?

Several randomized screening trials have demonstrated a reduction in CRC mortality by repeated FOBT followed by colonoscopy for positive test results. We did not find convincing evidence that screening tests other than FOBT / FIT have an effect on mortality. However, results from ongoing trials of other methods are underway – particularly on flexible sigmoidoscopy. A drawback of FOBT is the relatively low sensitivity, leaving a number of cancers undetected. It is hoped that other methods may be more accurate.

Endoscopy could offer an alternative method for the identification of polyps and early lesions. How effective this is in regard to reducing mortality from CRC and the incidence of CRC is not clear. In addition to the issue of effectiveness, factors such as cost, access, and acceptance, may limit the potential of colonoscopy for screening purposes. Future trials may also clarify these issues.

Computerized tomography is another method for identifying polyps and early lesions, but has similar limitations as colonoscopy in regard to cost, access, and acceptance. In addition, possible harm from radiation is a concern. As for the effectiveness of this method in preventing CRC incidence and mortality, no convincing evidence was found. Relevant ongoing trials are listed in a table within this report.

American researchers recently conducted a modelling exercise to estimate the impact of population screening programmes using different screening-methods. Their findings suggested that FOBT, sigmoidoscopy and colonoscopy will be approximately equally effective in life-years gained (82).

Screening Guidelines and Recommendations

Our overview of different national screening programs was largely based on information from three reports/articles that reviewed screening guidelines and programs within European countries and on international research initiatives on CRC-screening (4;39;51). Most of the countries that have implemented CRC screening at the national level as well as most screening programs at local level report using of FOBT as a screening tool at intervals of 1 to 2 years. Exceptions are Poland, which uses colonoscopy and Canada which uses flexible sigmoidoscopy as a primary screenings tool. Most countries recommend colonoscopy or flexible sigmoidoscopy if the FOBT is positive. For average-risk individuals at the population level, recommended screening ages range most often from 50 to 75 years. Japan offers screening for individuals over 40 years old. Some other countries do not recommend an upper age limit, but many countries do not recommend screening at older ages, typically after the mid-70s (39). The AHRQ-report concludes that the net benefits of screening are small for adults, age 76 to 85 years (10). Screening for CRC has a rapidly evolving science base, so guidelines may be expected to change as additional research results from ongoing studies become available.

Limitations of Screening

Screening has important ethical differences from clinical practice as the health service is targeting apparently healthy people. CRC screening has the potential to save lives or improve quality of life through early diagnosis of serious conditions, but it has certain limitations. Firstly, the risks directly related to the screening method warrants consideration. The primary established harms of CRC screening are due to the use of invasive procedures initially or in the evaluation sequence such as perforation due to endoscopy. The risk is likely to be small, but real. Also, the question of how screening recommendations should be modified or stratified based on a person's individual level of risk is an important consideration during the development of screening guidelines (1;3;21). Another downside of screening is related to the unavoidable problems with false positive and false negative results. To what extent false results impact negatively on health is not entirely clear. False positive results may trigger unnecessary investigations, which might be harmful, and there is also the possible harm from the psychological stress and uncertainty due to a positive test result.

Attendance rate

A key to success for any screening programme is a high attendance rate. To achieve this, it is necessary to acquire good understanding of barriers against screening. The barriers may be cultural of origin and therefore differ between countries (80). Those motivated through genetic predisposition may be eager to attend, while those at high-risk due to lifestyle may be more reluctant (81).

In USA where various screening modalities have been in use for more than a decade, there is a declining interest in FOBT screening in the population while colonoscopy

screening has gained popularity. In the Danish FOBT trial a mortality reduction was seen after 10 years of follow up, but this effect was no longer statistically significant after 17 year – probably due to a declining interest in participation over time.

The high proportion of false positive tests in FOBT screening programmes generates a high work-load due to the need for further investigations. In the USA 40-50% of all colonoscopies are performed as a consequence of screening, either as a primary screening activity or as a follow-up of positive results from other screening tests. This contribution is less than 5% in Norway, according to an unpublished survey by Gastronet (Geir Hoff – personal communication).

Implementing a national screening program

The implementation of a CRC screening is challenging particularly in regard to attendance rates, as the experience from many countries has shown. Two recent papers describe the planning of a CRC screening program and report the results of a feasibility study that was conducted to test an organizational model (78;79). The impact of a CRC screening program is directly related to its ability to involve the target population, to detect cancers and high grade adenomas, and to assure patient safety. Thus, the main challenges to address when planning and implementing a CRC screening program may be the following (78;79):

- Obtaining high attendance rates
- Deciding on which type of screening test to select and/or recommend
- The knowledge about, as well as attitudes towards, the program among the health professionals that are involved (GPs and gastroenterologists)
- Defining the GP's role in the screening program
- Assuring that sufficient resources for endoscopy and other additional workloads resulting from the screening program are available (whether endoscopy is used as the primary screening tool or only for follow-up investigations).

Well-planned and organized screening interventions have been associated with statistically greater results (70; 71).

Conclusions

Several randomized screening trials have demonstrated a reduction in CRC mortality by repeated FOBT testing followed by colonoscopy for positive test results.

There is so far no solid evidence on mortality reduction for the other primary screening tests that are available, but this will change with the reporting of findings from ongoing trials.

None of these screening methods seems to reduce incidence of CRC.

Most of the countries that have national CRC screening programs use stool tests (gFOBT or FIT) as the primary screening tests.

References

1. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134(5):1570-95.
2. Mandel JS. Screening of patients at average risk for colon cancer. *Med Clin North Am* 2005;89(1):43-59, vii.
3. SIGN. Management of colorectal cancer. A national clinical guidelines. Scottish Intercollegiate guideline network (SIGN); 2003.
4. Benson VS, Patnick J, Davies AK, Nadel MR, Smith RA, Atkin WS. Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. *Int J Cancer* 2008;122(6):1357-67.
5. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840 149 screening colonoscopies. *Gut* 2007;56(11):1585-9.
6. Eide TJ. Risk of Colorectal-Cancer in Adenoma-Bearing Individuals Within A Defined Population. *International Journal of Cancer* 1986;38(2):173-6.
7. Lance P. Colorectal cancer screening: confusion reigns. *Cancer Epidemiol Biomarkers Prev* 2008;17(9):2205-7.
8. Larsen IK, Småstuen M, Parkin DM, Bray F. Data Quality at the Cancer Registry of Norway. In: *Cancer in Norway 2006 - Cancer incidence, mortality, survival and prevalence in Norway*. Oslo: Cancer Registry of Norway, 2007.
9. Piper MA. Immunochemical versus guaiac fecal occult blood tests (DARE provisional record). 2004;26.
10. Whitlock E, Lin J, Liles E, Beil T, Fu R, O'Connor E, et al. Screening for Colorectal Cancer: An Updated Systematic Review. Rockville, Maryland: Agency for Healthcare Research and Quality; 2008. Evidence Synthesis No. 65, Part 1. October 2008.
11. Bray F, Wibe A, Dorum LM, Moller B. [Epidemiology of colorectal cancer in Norway]. *Tidsskr Nor Laegeforen* 2007;127(20):2682-7.
12. Kjellmo A, Drolsum A. [Diagnosis and staging of colorectal cancer]. *Tidsskr Nor Laegeforen* 2007;127(21):2824-8.

13. Cancer Research UK. Bowel Cancer [Cancer Research UK]. [updated 2007]. Available from: <http://www.cancerhelp.org.uk/help/default.asp?page=5912>.
14. European Union. Council Recommendation of 2 December 2003 on Cancer Screening. L327/34 [Official Journal of the European Union]. [updated 2003]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:327:0034:0038:EN:PDF>.
15. European Union Advisory Committee on Cancer Prevention. Recommendations on cancer screening in the European Union [European Union Advisory Committee On Cancer Prevention]. [updated 1999]. Available from: http://ec.europa.eu/health/ph_determinants/genetics/cancer_screening_en.pdf.
16. Malila N, Oivanen T, Hakama M. Implementation of colorectal cancer screening in Finland: experiences from the first three years of a public health programme. *Z Gastroenterol* 2008;46 Suppl 1:S25-S28.
17. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orłowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *New England Journal of Medicine* 2006;355(18):1863-72.
18. Goodyear SJ, Stallard N, Gaunt A, Parker R, Williams N, Wong L. Local impact of the English arm of the UK Bowel Cancer Screening Pilot Study. *Br J Surg* 2008;95(9):1172-9.
19. Zorzi M, Barca A, Falcini F, Grazzini G, Pizzuti R, Ravaioli A, et al. Screening for colorectal cancer in Italy: 2005 survey. *Epidemiologia & Prevenzione* 2007;31(2-3):49-60.
20. Sung J. Colorectal cancer screening: Its time for action in Asia. *Cancer Detect Prev* 2007;31(1):1-2.
21. World Gastroenterology Organisation (WGO) and the International Digestive Cancer Alliance. Practice guidelines: Colorectal cancer screening [WGO (World Gastroenterology Organisation)]. [updated 2007]. Available from: http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/o6_colorectal_cancer_screening.pdf.
22. Soares-Weiser K, Burch J, Duffy S, St John J, Smith S, Westwood M, et al. Diagnostic accuracy and cost-effectiveness of faecal occult blood tests (FOBT) used in screening for colorectal cancer: a systematic review (DARE provisional record). 2007;221.
23. Mayo Clinic. Colon Cancer: Improved Stool DNA Test [Mayo Clinic]. [updated 2008]. Available from: <http://www.mayoclinic.com/health/dna-stool-test/CO00018>.
24. NICE. Guidance on Cancer Services. Improving Outcomes in Colorectal Cancers. Manual Update. London: **National Institute for Clinical Excellence** ; 2004.
25. Brown SR, Baraza W, Hurlstone P. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database Syst Rev* 2007;(4):CD006439.

26. Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet* 2005;365(9456):305-11.
27. Hoff G, Bretthauer M, Huppertz-Hauss G, Kittang E, Stallemo A, Hoie O, et al. The Norwegian Gastronet project: Continuous quality improvement of colonoscopy in 14 Norwegian centres. *Scandinavian Journal of Gastroenterology* 2006;41(4):481-7.
28. Thiis-Evensen E, Hoff GS, Sauar J, Vatn MH. Patient tolerance of colonoscopy without sedation during screening examination for colorectal polyps. *Gastrointest Endosc* 2000;52(5):606-10.
29. Takahashi Y, Tanaka H, Kinjo M, Sakumoto K. Sedation-free colonoscopy. *Diseases of the Colon & Rectum* 2005;48(4):855-9.
30. National Cancer Institute (NCI). Colorectal cancer screening: Questions and answers [National Cancer Institute (NCI)]. [updated 2004]. Available from: <http://www.cancer.gov/cancertopics/factsheet/Detection/colorectal-screening>.
31. National Institutes of Health (NIH). Barium enema [National Institutes of Health (NIH)]. [updated 2008]. Available from: <http://www.nlm.nih.gov/medlineplus/ency/article/003817.htm>.
32. McFarland EG, Levin B, Lieberman DA, Pickhardt PJ, Johnson CD, Glick SN, et al. Revised colorectal screening guidelines: joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. *Radiology* 2008;248(3):717-20.
33. Lauenstein TC, Ajaj W, Kuehle CA. Virtual colonoscopy by MRI: state-of-the-art and future directions. *Gastrointest Endosc Clin N Am* 2005;15(4):797-811.
34. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO 1968. Number 34.
35. Gray JAM. Dimensions and definitions of screening. 1996.
36. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007;(1):CD001216.
37. Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J. The determinants of screening uptake and interventions for increasing uptake: a systematic review. *Health Technol Assess* 2001;4(14):i-vii.
38. Kerr J, Broadstock M, Day P, Hogan S. Effectiveness and cost-effectiveness of population screening for colorectal cancer: a systematic review of the literature (revised edition) (DARE structured abstract). Christchurch: New Zealand Health Technology Assessment (NZHTA) 2007;210.
39. Gutierrez-Ibarluzea I, Asua J, Latorre K. Policies of screening for colorectal cancer in European countries. *Int J Technol Assess Health Care* 2008;24(3):270-6.
40. Sundhedsstyrelsen M&MT. Screening for tarmkræft: Deltagelsesprocentens betydning – En medicinsk teknologivurdering [København:

Sundhedsstyrelsen, Monitorering & Medicinsk Teknologivurdering, 2008]; Medicinsk Teknologivurdering 2008; 10(1) [updated 2008]

41. Burch JA, Soares-Weiser K, St John DJB, Duffy S, Smith S, Kleijnen J, et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. *J Med Screen* 2007;14(3):132-7.
42. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. *Ann Intern Med* 2005;142(8):635-50.
43. Sosna J, Morrin MM, Kruskal JB, Lavin PT, Rosen MP, Raptopoulos V. CT colonography of colorectal polyps: a metaanalysis. *AJR Am J Roentgenol* 2003;181(6):1593-8.
44. Lewis JD, Ng K, Hung KE, Bilker WB, Berlin JA, Brensinger C, et al. Detection of proximal adenomatous polyps with screening sigmoidoscopy: a systematic review and meta-analysis of screening colonoscopy. *Arch Intern Med* 2003;163(4):413-20.
45. Halligan S, Altman DG, Taylor SA, Mallett S, Deeks JJ, Bartram C, I, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting (DARE structured abstract). *Radiology* 2005;237:893-904.
46. Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med* 2007;120(3):203-10.
47. Niv Y, Hazazi R, Levi Z, Fraser G. Screening Colonoscopy for Colorectal Cancer in Asymptomatic People: A Meta-Analysis. *Dig Dis Sci* 2008;
48. Walleser S, Griffiths A, Lord SJ, Howard K, Solomon MJ, Gebiski V. What is the value of computerized tomography colonography in patients screening positive for fecal occult blood? A systematic review and economic evaluation. *Clin Gastroenterol Hepatol* 2007;5(12):1439-46.
49. Mandel JS. Screening for colorectal cancer. *Gastroenterol Clin North Am* 2008;37(1):97-115, vii.
50. Zorzi M, Falcini F, Fedato C, Grazzini G, de' Bianchi PS, Senore C, et al. Screening for colorectal cancer in Italy: 2006 survey. *Epidemiol Prev* 2008;32(2 Suppl 1):55-68.
51. Bretthauer M, Hoff G. [Prevention and early diagnosis of colorectal cancer]. *Tidsskr Nor Laegeforen* 2007;127(20):2688-91.
52. Pox C, Schmiegell W, Classen M. Current status of screening colonoscopy in Europe and in the United States. *Endoscopy* 2007;39(2):168-73.
53. NGC. Colorectal cancer screening. Guideline from National Guideline Clearinghouse [<http://www.guideline.gov>]. The National Guideline Clearinghouse (NGC); [updated 2006]. Available from: http://www.guideline.gov/summary/summary.aspx?doc_id=9461&nbr=005066&string=colorectal+AND+screening#s23.
54. ICIS. Institute for Clinical Systems Improvement. Colorectal Cancer Screening (Guideline). [Institute for Clinical Systems Improvement]. [updated 2008]

55. NCCN practice guidelines in oncology 02-2008. Colorectal cancer screening. National Guideline Clearinghouse. In: 2008.
56. New Zealand Guideline. Screening to Improve Health in New Zealand [National Advisory Committee on Health and Disability(National Health Committee)]. [updated 2003]
57. UKFSST. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002;359(9314):1291-300.
58. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of Screening for Colorectal Cancer in the General Population. *JAMA: The Journal of the American Medical Association* 2000;284(15):1954-61.
59. Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. *Scand J Gastroenterol* 2003;38(6):635-42.
60. Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359(12):1207-17.
61. Lindholm E, Brevinge H, Haglund E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008;95(8):1029-36.
62. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992;84(20):1572-5.
63. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000;21(6 Suppl):273S-309S.
64. Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. *J Natl Cancer Inst* 2002;94(23):1763-72.
65. Segnan N, Senore C, Andreoni B, Arrigoni A, Bisanti L, Cardelli A, et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst* 2005;97(5):347-57.
66. Segnan N, Senore C, Andreoni B, Azzoni A, Bisanti L, Cardelli A, et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology* 2007;132(7):2304-12.
67. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol* 1999;34(4):414-20.
68. Weissfeld JL, Schoen RE, Pinsky PF, Bresalier RS, Church T, Yurgalevitch S, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J Natl Cancer Inst* 2005;97(13):989-97.

69. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;329(27):1977-81.
70. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008;103(6):1541-9.
71. Kerr J, Day P, Broadstock M, Weir R, Bidwell S. Systematic review of the effectiveness of population screening for colorectal cancer. *N Z Med J* 2007;120(1258):U2629.
72. Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326(10):653-7.
73. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001;345(8):555-60.
74. Walleser S, Griffiths A, Lord SJ, Howard K, Solomon MJ, Gebiski V. What is the value of computerized tomography colonography in patients screening positive for fecal occult blood? A systematic review and economic evaluation. *Clin Gastroenterol Hepatol* 2007;5(12):1439-46.
75. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007;357(22):2277-84.
76. Blue Cross Blue Shield Association. CT colonography ('virtual colonoscopy') for colon cancer screening (DARE structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS) 2004;17.
77. Blue Cross Blue Shield Association. Immunochemical versus guaiac fecal occult blood tests (DARE structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS) 2004;26.
78. Federici A, Barca A, Baiocchi D, Quadrino F, Valle S, Borgia P, et al. Can colorectal cancer mass-screening organization be evidence-based? Lessons from failures: the experimental and pilot phases of the Lazio program. *BMC Public Health* 2008;8:318.
79. DeGross A, Boehm J, Goode GS, Holden D, Seeff LC. Facilitators and challenges to start-up of the colorectal cancer screening demonstration program. *Prev Chronic Dis* 2008;5(2):A39.
80. Petersen GM. Barriers to preventive intervention. *Gastroenterol Clin North Am* 2002;31(4):1061-8.
81. Hoff G. Endoscopic screening for colorectal neoplasia in Norway. *International Journal of Cancer* 2002;32.
82. U.S. Preventive Services Task Force. Screening for colorectal cancer. US. Preventive Services Task Force Recommendation Statement. AHRQ publication 08-05124-EF-3, October 2008. <http://ahrq.gov/clinic/USPSTFo8/colocancer/colors.htm>

Appendices

1. SEARCH STRATEGY

CDSR - Cochrane Library

- #1 MeSH descriptor Colorectal Neoplasms explode all trees
- #2 (colorectal* or colon or colonic or bowel* or rectal or rectum or sigmoid or anal or anus) NEAR/3 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC):ti or (colorectal* or colon or colonic or bowel* or rectal or rectum or sigmoid or anal or anus) NEAR/3 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC):ab
- #3 (#1 OR #2)
- #4 MeSH descriptor Occult Blood explode all trees
- #5 MeSH descriptor Endoscopy, Gastrointestinal explode all trees
- #6 MeSH descriptor Colonoscopes explode all trees
- #7 MeSH descriptor Sigmoidoscopes explode all trees
- #8 MeSH descriptor Proctoscopes explode all trees
- #9 MeSH descriptor Immunochemistry explode all trees
- #10 MeSH descriptor Immunologic Tests explode all trees
- #11 faecal or fecal or (stool NEAR occult) or FOBTor FOB or haemoccult or hemoccult or sensa or coloscreen or seracult or (ez NEXT detect) or colocare or flexsure or hemmoquant or hemeselect or immudia or monohaem or insure or hemodia or (instant NEXT view) or innocare or magstream or (guaiac near/1 smear*) or endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (barium near/1 enema) or DCBE or immunologic* or immunodiagnos* or immunochemistry:ti or faecal or fecal or (stool NEAR occult) or FOBTor FOB or haemoccult or hemoccult or sensa or coloscreen or seracult or (ez NEXT detect) or colocare or flexsure or hemmoquant or hemeselect or immudia or monohaem or insure or hemodia or (instant NEXT view) or innocare or magstream or (guaiac near/1 smear*) or endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoido-

- scop* or COL or SIG or FSIG or (barium near/1 enema) or DCBE or immunologic* or immunodiagnos* or immunochemistry:ab
- #12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
- #13 MeSH descriptor Mass Screening, this term only
- #14 MeSH descriptor Population Surveillance, this term only
- #15 (screen* or test or tests or testing or tested or (population* near/1 surveillance) or (early near/3 detect*) or (early near/3 prevent*)):ti or (screen* or test or tests or testing or tested or (population* near/1 surveillance) or (early near/3 detect*) or (early near/3 prevent*)):ab
- #16 (#13 OR #14 OR #15)
- #17 (#3 AND #12 AND #16)

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- #1 MeSH descriptor Colorectal Neoplasms explode all trees
- #2 (colorectal* or colon or colonic or bowel* or rectal or rectum or sigmoid or anal or anus) NEAR/3 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenom* or lesion* or CRC)
- #3 (#1 OR #2)
- #4 MeSH descriptor Occult Blood explode all trees
- #5 MeSH descriptor Endoscopy, Gastrointestinal explode all trees
- #6 MeSH descriptor Colonoscopes explode all trees
- #7 MeSH descriptor Sigmoidoscopes explode all trees
- #8 MeSH descriptor Proctoscopes explode all trees
- #9 MeSH descriptor Immunochemistry explode all trees
- #10 MeSH descriptor Immunologic Tests explode all trees
- #11 faecal or fecal or (stool NEAR occult) or FOBTor FOB or haemoccult or hemocult or sensa or coloscreen or seracult or (ez NEXT detect) or colocare or flexsure or hemmoquant or hemeselect or immudia or monohaem or insure or hemodia or (instant NEXT view) or immocare or magstream or (guaiac near/1 smear*) or endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (barium near/1 enema) or DCBE or immunologic* or immunodiagnos* or immunochemistry
- #12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
- #13 MeSH descriptor Mass Screening, this term only
- #14 MeSH descriptor Population Surveillance, this term only
- #15 (screen* or test or tests or testing or tested or (population* near/1 surveillance) or (early near/3 detect*) or (early near/3 prevent*)):ti or (screen* or test or tests or testing or tested or (population* near/1 surveillance) or (early near/3 detect*) or (early near/3 prevent*)):ab
- #16 (#13 OR #14 OR #15)
- #17 (#3 AND #12 AND #16)

MEDLINE Ovid

1. exp Colorectal Neoplasms/
2. ((colorectal\$ or colon or colonic or bowel\$ or rectal or rectum or sigmoid or anal or anus) adj3 (cancer\$ or neoplas\$ or tumor\$ or tumour\$ or carcinoma\$ or sarcoma\$ or adenocarcinoma\$ or adeno?carcinoma\$ or adenom\$ or lesion\$ or CRC)).tw.
3. 1 or 2
4. exp Occult Blood/
5. exp Endoscopy, Gastrointestinal/
6. exp Colonoscopes/
7. exp Sigmoidoscopes/
8. exp Proctoscopes/
9. exp Immunochemistry/
10. exp Immunologic Tests/
11. (faecal or fecal or stool occult or FOBTor FOB or haemoccult or hemoccult or sensa or coloscreen or seracult or ez detect or colocare or flexsure or hemmoquant or hemeselect or immudia or monohaem or insure or hemodia or instant view or immocare or magstream or (guaiac adj2 smear\$) or endoscop\$ or proctoscop\$ or colonoscop\$ or sigmoidoscop\$ or rectosigmoidoscop\$ or proctosigmoidoscop\$ or COL or SIG or FSIG or (barium adj2 enema) or DCBE or immunologic\$ or immuno-diagnos\$ or immunochemistry).tw.
12. or/4-11
13. Mass Screening/
14. Population Surveillance/
15. (screen\$ or test or tests or testing or tested or (population\$ adj2 surveillance) or (early adj3 detect\$) or (early adj3 prevent\$)).tw.
16. or/13-15
17. 3 and 12 and 16
18. limit 17 to "reviews (specificity)

2. ONGOING CLINICAL TRIALS

Study Title	Study Sponsors	Clinical Trials. gov Identifier	Study Start Date	Year Completed or Expected Completion Date	Number of Participants	Age of Participants (Years)	Study Type and Design	Screening Tests Involved	Brief Description
NORCCAP: Norwegian Colorectal Cancer Prevention Trial - Norway (Oslo and Telemark)	Norwegian Department of Health and Social Affairs, Norwegian Cancer Society	NCT00119912	January 1999	Ongoing (January 2017)	100000	50 to 64	Interventional Prevention, Randomized, Active Control, Safety/Efficacy Study	Flexible sigmoidoscopy, FOBT	Study whether or not flexible sigmoidoscopy screening will reduce large bowel cancer and cancer deaths and if the addition of FOBT screening will also help reduce the mortality rate
Screening Tests in Detecting Colorectal Cancer (Colorectal Cancer Screening: Fecal Blood vs. DNA) - USA	Mayo Clinic, National Cancer Institute (NCI), North Central Cancer Treatment Group	NCT00025025	October 2001	Ongoing (NS)	4000 (projected figure)	50 to 64 (included in accrual prior to June 5, 2003) and 65 to 80	Interventional Screening, Randomized, Active Control	FOBT, DNA-based testing of stool and blood, colonoscopy	Compare effectiveness (sensitivity, specificity, and predictive values) of FOBT and DNA-based testing (MTAP) of stool and blood in identifying colorectal cancer

Study Title	Study Sponsors	Clinical Trials. gov Identifier	Study Start Date	Year Completed or Expected Completion Date	Number of Participants	Age of Participants (Years)	Study Type and Design	Screening Tests Involved	Brief Description
Screening for Cancer of the Prostate, Lung, Colon, Rectum, or Ovaries (PLCO) in Older Patients - USA	NCI	NCT00002540	November 1993	Ongoing (NS)	74000 women, 74000 men (projected)	55 to 74	Interventional Randomized study, Screening	Flexible sigmoidoscopy	Randomized trial to investigate whether screening methods used to detect prostate, lung, colon, rectal, or ovarian cancer can reduce deaths from these cancers
A Follow-up Colonoscopy Examination in Patients who Had Previously Undergone Screening Colonoscopy - China	Chinese University of Hong Kong -- Hong Kong, China	NCT00280332	March 2006	November 2007	560	50 to 75	Observational Case control, Prospective	Colonoscopy	“To determine the prevalence of colonic neoplasm in patients who had previously undergone screening colonoscopy,” to determine appropriate intervals for re-screening for people with average risk, and to determine characteristics that predict recurrence of adenoma
Is Barium Enema an Adequate Diagnostic Tests for Patients with Positive FOBT? (DCBE) – Location Not Stated	VA Caribbean Healthcare system	NCT00619814	September 2003	October 2005	50	50 to 80	Interventional Diagnostic, Single Blind, Single Group Assignment, Safety/Efficacy Study	Double contrast barium enema, Colonoscopy, FOBT	Determine whether double contrast barium enema is a suitable alternative to colonoscopy for the evaluation of patients with positive FOBT

Study Title	Study Sponsors	Clinical Trials. gov Identifier	Study Start Date	Year Completed or Expected Completion Date	Number of Participants	Age of Participants (Years)	Study Type and Design	Screening Tests Involved	Brief Description
Long-term Follow-up Study Designed to Evaluate the Relative Risk of Two Colonoscopy Schedules for Patients with Small Polyps -USA	Department of Veterans Affairs (Central Lab-Tucson, AZ)	NCT 00032344	October 1993	February 2007	3000	50 to 75	Interventional Diagnostic, Non-Randomized, Active Control, Single Group Assignment, Efficacy Study	Colonoscopy	Determine risk factors that can be used to target more sensitive screening tests (colonoscopy) towards people with higher risk for colon cancer
Colorectal Neoplasia Screening in Asymptomatic Women at Regional Navy/Army Medical Centers: The CON-CeRN --USA	NCI	NCT 00339950	February 2000	Data Analysis Phase ongoing (Study conclusion date not stated)	937	40 to 79 (women only)	Observational	Colonoscopy, Flexible Sigmoidoscopy	Determine how many advanced colon cancers will be missed if only sigmoidoscopies are performed instead of full colonoscopies
Comparison of Barium Enema, Computed Tomographic Colonography, and Colonoscopy in Detecting Colon Cancer -- USA	Duke University	NCT 00016029	August 2000	Ongoing (NS)	2133	18 and older	Interventional Diagnostic	Air contrast barium enema, CT colonography, Colonoscopy, FOBT	Compare the effectiveness of air contrast barium enema, CT colonography, and colonoscopy in detecting colon cancer in patients with positive FOBT or with other risk factors

Study Title	Study Sponsors	Clinical Trials. gov Identifier	Study Start Date	Year Completed or Expected Completion Date	Number of Participants	Age of Participants (Years)	Study Type and Design	Screening Tests Involved	Brief Description
Computed Tomographic Colonography in Screening Healthy Participants for Colorectal Cancer (National CT Colonography Trial) -USA	American College of Radiology Imaging Network, NCI	NCT00084929	February 2005	Ongoing (NS)	2607	50 and older	Interventional Screening	CT colonography (virtual colonoscopy), Colonoscopy	Study effectiveness of CT colonography (in comparison to colonoscopy) for screening healthy people for large colorectal lesions
Detection of Colorectal Cancer in Peripheral Blood by Septin 9 DNA Methylation Assay - Germany and Hungary	Epigenomics, Inc.	NCT00696345	January 2005	February 2007	700	40 and older	Observational Case control, Prospective	Colonoscopy, Colon cancer screening assay to detect colon cancer DNA in blood plasma	Testing and development of colon cancer screening assay to detect colon cancer DNA in blood plasma