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Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals (Review)

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[Intervention Review]

Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals

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ABSTRACT

Background

Colorectal cancer is the third most frequent cancer in the world. As the sojourn time for this cancer is several years and a good prognosis is associated with early stage diagnosis, screening has been implemented in a number of countries. Both screening with faecal occult blood test and flexible sigmoidoscopy have been shown to reduce mortality from colorectal cancer in randomised controlled trials. The comparative effectiveness of these tests on colorectal cancer mortality has, however, never been evaluated, and controversies exist over which test to choose.

Objectives

To compare the effectiveness of screening for colorectal cancer with flexible sigmoidoscopy to faecal occult blood testing.

Search methods

We searched MEDLINE and EMBASE (November 16, 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 11) and reference lists for eligible studies.

Selection criteria

Randomised controlled trials comparing screening with flexible sigmoidoscopy or faecal occult blood testing to each other or to no screening. Only studies reporting mortality from colorectal cancer were included. Faecal occult blood testing had to be repeated (annually or biennially).

Data collection and analysis

Data retrieval and assessment of risk of bias were performed independently by two review authors. Standard meta-analyses using a random-effects model were conducted for flexible sigmoidoscopy and faecal occult blood testing (FOBT) separately and we calculated relative risks with 95% confidence intervals (CI). We used a Bayesian approach (a contrast-based network meta-analysis method) for indirect analyses and presented the results as posterior median relative risk with 95% credibility intervals. We assessed the quality of evidence using GRADE.

Main results

We identified nine studies comprising 338,467 individuals randomised to screening and 405,919 individuals to the control groups. Five studies compared flexible sigmoidoscopy to no screening and four studies compared repetitive guaiac-based FOBT (annually and biennially) to no screening. We did not consider that study risk of bias reduced our confidence in our results. We did not identify any studies comparing the two screening methods directly. When compared with no screening, colorectal cancer mortality was lower with flexible sigmoidoscopy (relative risk 0.72; 95% CI 0.65 to 0.79, high quality evidence) and FOBT (relative risk 0.86; 95% CI 0.80 to 0.92, high quality evidence). In the analyses based on indirect comparison of the two screening methods, the relative risk of dying from colorectal cancer was 0.85 (95% credibility interval 0.72 to 1.01, low quality evidence) for flexible sigmoidoscopy screening compared to FOBT. No complications occurred after the FOBT test itself, but 0.03% of participants suffered a major complication after follow-up. Among more than 60,000 flexible sigmoidoscopy screening procedures and almost 6000 work-up colonoscopies, a major complication was recorded in 0.08% of participants. Adverse event data should be interpreted with caution as the reporting of adverse effects was incomplete.

Authors' conclusions

There is high quality evidence that both flexible sigmoidoscopy and faecal occult blood testing reduce colorectal cancer mortality when applied as screening tools. There is low quality indirect evidence that screening with either approach reduces colorectal cancer deaths more than the other. Major complications associated with screening require validation from studies with more complete reporting of harms.

PLAIN LANGUAGE SUMMARY

Comparison of two methods used in screening for colorectal cancer

Cancer in the large intestine (colon) and rectum is one of the most frequent cancers in developed countries. The disease develops from benign lesions over a time span of about 10 years. If the lesion has turned into cancer, the prognosis is far better if the disease is detected at an early stage. Screening and detection for early cancers and benign precursors may therefore reduce the number of deaths caused by this disease. Cancers and benign precursors may bleed, and the blood can be detected in the stool by specific tests, the so-called faecal occult blood tests (FOBT). If the test is positive (that is blood is detected), the person will be offered a colonoscopy to find the source of bleeding. Unfortunately, FOBT fails to discover a considerable number of cancers and precursor lesions. Therefore, endoscopic examination of the rectum and lower large intestine (the sigmoid colon) has been advocated (called flexible sigmoidoscopy). Flexible sigmoidoscopy is performed with a flexible instrument inserted through the anus and introduced about 50 centimetres into the lower large intestine after cleansing with a small enema. This allows direct visual inspection of the interior wall of the intestine, and benign lesions and malignant tumours may be detected. Benign lesions may be removed in the same session without anaesthesia and without any discomfort for the patient, and a follow-up colonoscopy may be offered.

The purpose of this review was to compare the two screening methods (FOBT and flexible sigmoidoscopy) in their ability to reduce the number of deaths due to cancer in the large intestine and rectum.

We identified four trials which compared FOBT to no screening and five trials which compared flexible sigmoidoscopy to no screening. No studies compared the two methods directly. Mortality from colorectal cancer was reduced with FOBT screening and screening with flexible sigmoidoscopy. When we compared the two methods, we could not conclude that one was better than the other.

No complications occurred after the FOBT test itself, but 0.03% of participants suffered a major complication after follow-up. Among more than 60,000 flexible sigmoidoscopy screening procedures and almost 6000 work-up colonoscopies, a major complication was recorded in 0.08% of participants. These findings should be interpreted with caution as the reporting of adverse effects was incomplete.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Flexible sigmoidoscopy or faecal occult blood testing compared with care as usual for colorectal cancer screening

Patient or population: Asymptomatic individuals
Settings: Participants recruited among volunteers or randomly chosen from public registries
Intervention: Flexible sigmoidoscopy once only or repeated faecal occult blood testing
Comparison: Care as usual

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No screening	Screening group				
CRC Mortality - Flexible sigmoidoscopy	8 per 1000	6 per 1000 (5 to 6)	RR 0,72 (0.65 to 0.79)	414,744 (5 studies)	⊕⊕⊕⊕ high	
CRC Mortality - Faecal occult blood testing	8 per 1000	7 per 1000 (6 to 7)	RR 0,86 (0.80 to 0.92)	329,642 (4 studies)	⊕⊕⊕⊕ high	
CRC incidence - Flexible sigmoidoscopy	20 per 1000	16 per 1000 (15 to 18)	RR 0,82 (0.73 to 0.90)	414,744 (5 studies)	⊕⊕⊕◯ moderate[2]	
CRC incidence - Faecal occult blood testing	20 per 1000	19 per 1000 (18 to 20)	RR 0,95 (0,88 to 1,02)	329,536 (4 studies)	⊕⊕⊕⊕ high	
All-cause Mortality - Flexible sigmoidoscopy	254 per 1000	249 per 1000 (241 to 257)	RR 0,98 (0.95 to 1.01)	364,827 (4 studies)	⊕⊕⊕⊕ high	
All-cause Mortality - Faecal occult blood testing	254 per 1000	254 per 1000 (251 to 257)	RR 1,00 (0,99 to 1,01)	329,642 (4 studies)	⊕⊕⊕⊕ high	

CI: Confidence interval; **RR:** Risk Ratio; **CRC:** Colorectal cancer

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Assumed risk is computed by combining events and participants in the control groups in all trials. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[2] Evidence downgraded one level due to heterogeneity between trials. This heterogeneity may be explained by shorter follow-up of the Norwegian NORCCAP trial, but other explanations like study design cannot be ruled out.

BACKGROUND

Description of the condition

With more than 550,000 annual deaths, colorectal cancer (CRC) is a major health problem in industrialized countries. CRC is the most frequent malignant disease diagnosed in Europe (Ferlay 2010) and the third most frequent cancer in the United States (Jemal 2009). Most cases of CRC develop in so-called average risk individuals, that is in individuals without any known CRC risk factors. To date, the lifetime risk for colorectal cancer for average-risk individuals in industrialized countries is about 5%. Five-year survival of people with colorectal cancer exceeds 90% if the disease is diagnosed at an early stage, but only about 60% for patients with lymph node involvement and under 10% if distant organ metastases are present (Ries 2007).

Description of the intervention

Testing for faecal occult blood has been extensively studied, and a variety of commercial tests are available. These tests are based on either detecting peroxidase activity of the haeme moiety of the haemoglobin molecule (guaiac tests, FOBT) or immunochemical methods (faecal immunological test, FIT) that are specific towards the globin part of the human haemoglobin.

Screening for CRC has been implemented in a number of countries. Testing for faecal occult blood (FOBT), flexible sigmoidoscopy and colonoscopy are used as screening tools. The only two modalities that have been tested in randomised trials are FOBT and flexible sigmoidoscopy, but despite this, colonoscopy is regarded the gold standard in CRC screening. The obvious advantage of colonoscopy as a screening tool is the direct visualisation of the entire colonic mucosa, but this may be a false reassurance. Several case-control studies have indicated that colonoscopy does not affect CRC mortality and the presence of advanced adenomas in the colon proximal to the splenic flexure (Baxter 2009; Brenner 2010).

How the intervention might work

As clinical symptoms develop late in the course of the disease, early detection is often not achieved in individuals with symptoms. It is believed that the majority of colorectal cancers develop from benign precursor lesions, the so-called adenomatous polyps or adenomas, through a series of genetic changes (adenoma-carcinoma sequence) during a time interval of at least five to 10 years (Muto 1975; Vogelstein 1988). Therefore, CRC is considered a good target for screening.

Why it is important to do this review

As the FOBT and flexible sigmoidoscopy have never been directly compared by means of CRC mortality in prospective studies, uncertainty still exists regarding which test to choose. Both tests have limitations. For example, sensitivity for both CRC and adenoma detection is lower for FOBT compared to flexible sigmoidoscopy, but only half of the colon is examined with the latter, which means that about one third of neoplasias (CRCs and adenomas) that are located in the proximal colon may be missed (Anderson 2004). FOBT is performed at home without any absenteeism from work, and reading of the tests may be automated (FIT only). Flexible sigmoidoscopy is labour demanding, and its invasive nature may lead to lower compliance with screening (Hol 2010) and higher complication rates.

There are four large randomised, controlled studies which have established the effectiveness of FOBT (Mandel 1993; Hardcastle 1996; Kronborg 1996; Lindholm 2008) and the results have been pooled in a Cochrane review (Hewitson 2007). This review showed a reduction in mortality from CRC by 16% due to screening, but no reduction in CRC incidence or all-cause mortality. Until recently, flexible sigmoidoscopy had only been evaluated in one small-scale randomised controlled trial. This study from Norway showed an 80% decrease in CRC incidence in the screening group after 13 years, but a disturbing 57% increase in all-cause mortality (Thiis-Evensen 1999) compared to a no-screening control group. In the last years, four large randomised trials of CRC screening by flexible sigmoidoscopy have been published (Hoff 2009; Atkin 2010; Segnan 2011; Schoen 2012). A reduction in CRC mortality of 22% to 31% was observed in the screening groups compared to the no-screening control groups. The three latter studies also found a reduced incidence of CRC by 18% to 23%, respectively, but no effect on all-cause mortality.

Therefore, whether to implement the low-cost non-invasive FOBT or the invasive and relatively resource-demanding flexible sigmoidoscopy is an area of controversy. The scope of this review is to compare these modalities when applied as screening tools in asymptomatic individuals in randomised controlled trials.

OBJECTIVES

The purpose of this review was to identify randomised controlled trials of FOBT or flexible sigmoidoscopy as a CRC screening modality in an asymptomatic population and to compare the effectiveness on colorectal cancer (CRC) mortality for these two methods.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials of CRC screening reporting mortality from CRC in individuals invited for screening with flexible sigmoidoscopy versus FOBT or with any of these versus no screening. As FOBT screening requires repetitive testing, only studies investigating FOBT that included repetitive stool-testing (annually or biennially) were considered. Studies that were only reported as abstracts without full-paper publication were not included. There was no restriction with regard to publication language. Data from trials that were published on several occasions due to increasing length of follow-up were analysed once only, and only data from the latest publication were included in the main analyses. Quasi-randomised trials were not included.

Types of participants

Adult (18 years and older) asymptomatic individuals participating in a CRC screening trial with either FOBT or flexible sigmoidoscopy. Participants could be recruited either as volunteers or identified through population or general practitioners' registries.

Types of interventions

CRC screening with FOBT or flexible sigmoidoscopy. For FOBT, both guaiac-based and immunological tests were included. The guaiac test slides were or were not rehydrated. For the flexible sigmoidoscopy trials, trials using rigid endoscopes were excluded.

Types of outcome measures

Primary outcomes

- CRC mortality

Studies not reporting CRC mortality were excluded from the review.

Secondary outcomes

- CRC incidence
- All-cause mortality
- Attendance rates
- Adverse effects
- CRC staging
- Use of endoscopy work-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 11), MEDLINE and EMBASE (until 16 November 2012) for eligible papers. Separate searches were performed for faecal occult blood test (FOBT) and flexible sigmoidoscopy trials for each database. The reference lists of all relevant retrieved studies were searched for additional trials. In addition, we searched the reference list of the Cochrane review of CRC screening using FOBT (Hewitson 2007).

The comprehensive search strategy was developed by the authors and the Trials Search Co-ordinator at the Cochrane Colorectal Cancer Group, Copenhagen, Denmark, and is available in the appendix section: MEDLINE searches (Appendix 1; Appendix 2); EMBASE searches (Appendix 3; Appendix 4); CENTRAL searches Appendix 5; Appendix 6). The first search was performed in January 2011 and was updated November 16, 2012.

Data collection and analysis

Selection of studies

One investigator (OH) excluded obviously irrelevant titles from the first search. Two authors (OH and MB) independently considered the remaining abstracts and potentially relevant full-text articles were obtained. The same authors independently considered the full-text manuscripts according to the pre-specified inclusion and exclusion criteria. Disagreement was resolved by consensus.

Data extraction and management

Data were extracted from the included studies into an electronic data sheet by OH and MB working independently and were finally compared. Discrepancies were addressed and solved by re-reviewing the papers together. The abstracted data included the study citation, study design, country, methods of randomisation and allocation concealment, type of intervention, definition of positive screening test, length of follow-up, inclusion and exclusion criteria, participants' characteristics, number of individuals randomised, number of excluded participants, participants lost to follow-up, compliance with screening, blinding of outcome assessment, number of new cases of CRC, mortality from CRC, mortality from all causes, staging of CRC, adverse effects due to the screening procedure, use of endoscopic and radiologic work-up after a positive screening test and funding.

Assessment of risk of bias in included studies

The methodologic quality of the included trials was assessed by two independent review authors (OH and MB) according to the Cochrane Collaboration's Risk of Bias tool(Higgins 2008). Disagreement was resolved by consensus. We included a description and assessment of the risk of bias associated with generation of the randomisation sequence, allocation concealment, blinding, incomplete outcome data, selective reporting of data and other potential threats to validity for each of the included studies. Risk of bias in the included studies was explicitly judged for each of these domains and categorized as 'low risk', 'high risk' or 'unclear' of bias, if information was insufficient to assess risk.

If at least one of the six domains was assessed as being at 'high risk of bias' for a trial then the aggregate risk of bias for that trial was set as high.

Measures of treatment effect

We calculated and reported risk ratios (RR) with corresponding 95% credibility intervals (from a Bayesian network meta-analysis model) on an intention-to-treat basis for all outcomes. In addition, we performed traditional pair-wise comparisons for FOBT and flexible sigmoidoscopy trials separately for all outcomes and reported relative risk with 95% confidence intervals (CI).

Unit of analysis issues

Cluster randomised trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This can cause type I errors (Bland 1997; Gulliford 1999).

Where clustering was not accounted for in the primary studies, this was specified in the footnote of the analysis to indicate the presence of a possible unit of analysis error. We contacted the first authors of studies to obtain the intra-class correlation coefficient of their clustered data and to adjust for this by using the effective sample size method (Section 16.3.4 in Higgins 2008). We additionally performed a sensitivity analysis in which cluster randomised trials were excluded.

Dealing with missing data

All analyses were carried out on an intention-to-treat basis; that is, participants were analysed according to their allocated treatment (irrespective of whether they adhered to the screening intervention or not). For participants lost to follow-up it was assumed that the relevant events (CRC death, death due to any reason, or CRC) did not occur.

Assessment of heterogeneity

We assessed heterogeneity separately for each paired comparison of two different screening strategies, on the basis of the *Cochrane Handbook for Systematic Reviews of Interventions* recommendations (I^2 values of 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) (Higgins 2008). In addition to the I^2 measurement we presented the χ^2 and its P value and considered the direction and magnitude of the treatment effects. As the χ^2 test in a meta-analysis with few studies is underpowered to detect heterogeneity should it exist, a P value of 0.10 was used as the threshold of statistical significance.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of the results. These biases include publication bias and selective outcome reporting bias. Funnel plots can be useful in assessing reporting biases. We intended only to produce funnel plots and apply Peters' test for asymmetry (Peters 2006) for outcome measures which included at least 10 studies of different sizes, as suggested by Higgins 2008.

Data synthesis

The analysis was based on the method of multiple treatment meta-analysis (MTM) as described by Salanti 2007. We used the contrast-based network meta-analyses method proposed by Salanti et al (a Bayesian method based on the Markov Chain Monte Carlo simulation). All MTMs were performed using Winbugs version 1.4.3 (Imperial College and MRC, UK) utilizing random effects models. The estimates obtained by generating three chains with 10,000 initial iterations (burn in) and 50,000 iterations were used for the estimations. All results for the MTM were reported as posterior median with corresponding 95% credibility intervals (CrI). We only combined studies in meta-analyses if we found that the studies were sufficiently similar to each other with regard to population, context, and method of implementation of the screening intervention.

In addition to the estimates of effect based on the MTM analysis, we also presented results from traditional pair-wise comparisons for FOBT and flexible sigmoidoscopy against 'no screening' separately. Results were presented as relative risk with 95% confidence interval (CI).

We assessed the quality of the evidence as high, moderate, low or very low using the GRADE approach (Schünemann 2008) and have presented the results in the 'Summary of findings' table. In the absence of formal guidance regarding the application of GRADE to network meta-analysis, we have downgraded the quality of evidence by default for indirectness where network meta-analysis results are based solely on indirect evidence.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were planned.

Sensitivity analysis

MTM aggregates both direct (i.e. from the same trial) and indirect (i.e. from different trials) evidence to an aggregate estimate of effect for a comparison between two interventions. We intended to apply sensitivity analyses excluding indirect evidence in the event of using both indirect and direct evidence comparing FOBT and flexible sigmoidoscopy. As follow-up was very different among the trials, we performed a 10-year follow-up sensitivity analysis. In this analysis, only the endoscopy screening trials and the FOBT trials with approximately 10 years of follow-up were compared.
Furthermore, we performed sensitivity analyses in which cluster randomised trials were excluded. We also performed sensitivity analyses where trials that were assessed as being at high risk of bias (the aggregate assessment across all six domains) were excluded. Finally, we decided to conduct an analysis where we excluded results from annual FOBT screening, that is we only included biennial FOBT screening, which is the most widely used approach.

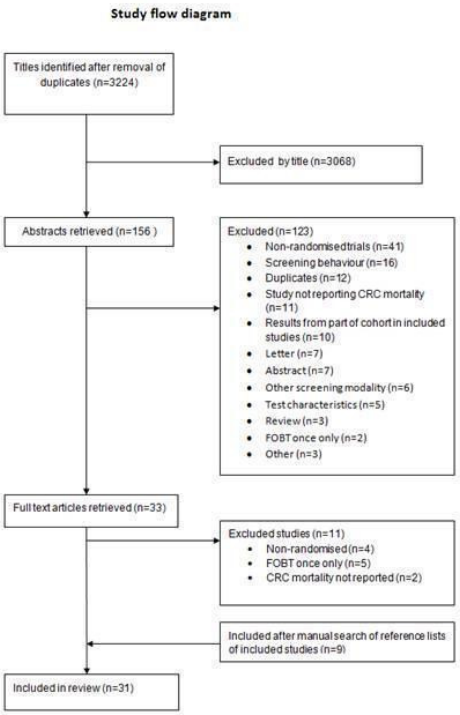
RESULTS

Description of studies

Results of the search

Our literature search identified 3224 titles, and abstracts were obtained for 155 of these (Figure 1). Following the reading of the abstracts, 33 full-text articles were retrieved and considered for inclusion. Ten were subsequently excluded (see Characteristics of excluded studies) leaving 22 manuscripts for inclusion in the final analyses and one trial which was identified as ongoing (Paimela 2010). After manual searching of the reference lists of the included papers, an additional nine studies were included, all addressing physical and psychological adverse effects of the screening procedures (Lindholm 1997; Schoen 2000; Taylor 2000; Hoff 2001; Larsen 2002; Parker 2002; Miles 2003; Wardle 2003; Larsen 2007). In addition, we contacted the corresponding authors of the Swedish and Italian trials to obtain further information.

Figure 1.



Included studies

Nine separate trials were included in the review, but due to the multiple reports that they have generated, we report on the characteristics of 31 separate study comparisons in Characteristics of included studies and Table 1. Eleven reports from four randomised controlled trials that reported on mortality or the incidence of CRC on repeated FOBT versus no screening were identified: one Swedish (Kewenter 1994; Lindholm 2008), one Danish (Kronborg 1996; Jorgensen 2002; Kronborg 2004), one English (Hardcastle 1996; Scholefield 2002; Scholefield 2012) and one from the US (Mandel 1993; Mandel 1999; Mandel 2000). Due to the pre-specified inclusion criteria, only the latest reports (with the longest follow-up) were included in the main meta-analysis.

Flexible sigmoidoscopy versus no screening was evaluated in five randomised controlled trials: one British (Atkin 2010), one Italian (SCORE, Screening COlon Rectum) (Segnan 2011), one from the US (PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial) (Schoen 2012) and two Norwegian trials (TPS, Telemark Polyp Study (Hoff 1996; Thiis-Evensen 1999) and the Norwegian Colorectal Cancer Prevention (NORCCAP) trial (Hoff 2009)). We did not identify any trials comparing FOBT and flexible sigmoidoscopy directly with respect to mortality from CRC. Fourteen papers reporting adverse effects in the identified screening trials were included (Kewenter 1996; Lindholm 1997; Robinson 1999; Taylor 2000; Schoen 2000; Hoff 2001; Atkin 2002; Larsen 2002; Parker 2002; Segnan 2002; Gondal 2003; Miles 2003; Wardle 2003; Larsen 2007).

Faecal occult blood trials

Altogether, the four FOBT trials included 172,734 individuals in the screening groups and 156,908 in the control groups (Mandel 1999; Kronborg 2004; Lindholm 2008; Scholefield 2012). Individuals were aged 45 to 80 years. All participants were randomised either on an individual basis or by household. The US study (Mandel 1999) included volunteers to the study, while the other three invited participants from public registries. All FOBT trials used a guaiac-based test. The test was rehydrated in the majority of cases in the US (Mandel 1999) and Swedish (Lindholm 2008) trials, but not in Denmark (Kronborg 2004) and England (Scholefield 2012). Dietary restrictions were applied in all trials except the Swedish trial (Lindholm 2008). In the US and Danish trials (Mandel 1999; Kronborg 2004), all participants with at least one positive test slide out of six were referred for diagnostic work-up. In the English trial (Scholefield 2012) and among 44% of participants in the Swedish trial (Lindholm 2008) an initial positive FOBT was investigated through a second FOBT, and those who tested positive the second time were referred for a diagnostic work-up. Work-up included full colonoscopy, except in the Swedish trial (Lindholm 2008) where a flexible sigmoidoscopy and double contrast barium enema was applied. Biennial screening was offered in the Danish (Kronborg 2004) and English (Scholefield 2012) trials throughout the study period. In the US study (Mandel 2000), participants in the intervention group were randomised 1:1 to biennial or annual screening. There was a three to five year hiatus in the screening period in this trial. Originally the trial ended in 1982, but due to lower than expected CRC mortality in the control group, screening was re-instituted in 1986 and this second phase ended in 1992. In the Swedish trial (Lindholm 2008), three cohorts of participants were included at different time points. All these cohorts had their own screening schedule. Two cohorts had re-screening 21 to 24 months after the first FOBT. These cohorts were included in the biennial screening analyses. The last cohort had two re-screenings with an 18 months interval after the initial screen, and this cohort was only included in the analysis considering all FOBT trials. The number of offered screening rounds varied between the FOBT studies. Nine rounds were offered in the Danish trial (Kronborg 2004), but only participants in the preceding round were invited for further screening. A no re-invitation procedure was initially also applied in the English trial (Scholefield 2012), but was abandoned half-way through the study in an effort to increase compliance with screening, resulting in an offer to be screened for three to six rounds. In the Swedish trial (Lindholm 2008), screening was offered two to three times in the different cohorts. The annual screening group was invited for 11 screening rounds in the US trial (Mandel 2000), and six rounds were offered to the biennial screening group. Follow-up was reported after 18 and 17 years in the US (Mandel 2000) and Danish (Kronborg 2004) FOBT trials, and after a median of 19.5 years in the English trial (Scholefield 2012) and 15.5 years in the Swedish trial (Lindholm 2008). Participants with known prior CRC were excluded in all trials.

Flexible sigmoidoscopy screening trials

In the five identified trials, 165,733 individuals were randomised to flexible sigmoidoscopy and 249,011 individuals comprised the control groups who received care as usual. Four trials applied a once-only screening intervention (one screening flexible sigmoidoscopy only for each participant) (Thiis-Evensen 1999; Hoff 2009; Atkin 2010; Segnan 2011), while the US trial offered the screening group a second flexible sigmoidoscopy three to five years after the first (Schoen 2012). Eligible individuals were aged 50 to 74 years. Time to follow-up for the primary outcome was different between the trials. Median follow-up for CRC mortality was six

years in the largest Norwegian trial (Hoff 2009), and 11.2, 11.4 and 11.9 years in the British (Atkin 2010), Italian (Segnan 2011) and US (Schoen 2012) trials, respectively. The smaller Norwegian trial (Thiis-Evensen 1999) reported mortality from CRC after 13 years of follow-up. All trials referred screening-positive individuals to colonoscopy work-up, but the definition of a positive test varied between the studies. In the US trial (Schoen 2012), finding of any lesion or mass during screening qualified for colonoscopy referral to the individual's primary care physician for follow-up. In the British trial (Atkin 2010), a positive test was defined as the finding of any polyp 10 mm in diameter or larger, advanced adenoma (tubulovillous or villous histology, severe dysplasia or three or more adenomas) irrespective of size, more than 20 hyperplastic polyps proximal to the rectum, or invasive cancer. The Italian trial (Segnan 2011) applied the same definition as the British trial, with the exception that individuals with any polyp larger than 5 mm in diameter were also referred to colonoscopy. The large Norwegian trial (Hoff 2009) biopsied all polyps at the initial screen and referred all individuals with histologically verified adenomas for work-up, irrespective of size, and all individuals who harboured a polyp 10 mm in diameter or larger (irrespective of histology). In addition, half of the individuals in the screening group were randomly allocated to provide a FIT as well. Individuals with a positive FIT, irrespective of the result of the screening flexible sigmoidoscopy, were offered work-up colonoscopy. In the small Norwegian study, all individuals with any polyp were offered colonoscopy (Thiis-Evensen 1999).

Excluded studies

See Characteristics of excluded studies. Ten trials were excluded from the review: five trials assessed the effect of FOBT on one occasion only (Berry 1997; Brevinge 1997; Rasmussen 1999; Li 2003; Zheng 2003); three trials were non-randomised studies (Winawer 1993; Faivre 2004; Denis 2009); one had a quasi-randomised design and used a rigid endoscope (Selby 1988); and one trial did not report the predefined primary outcome (Thiis-Evensen 2001).

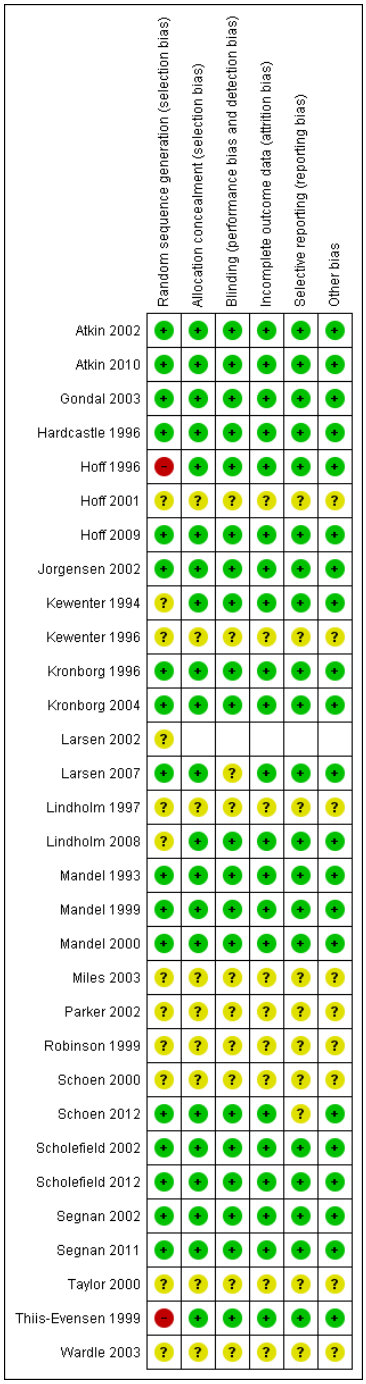
Ongoing studies

See Characteristics of ongoing studies. The search identified one ongoing trial: in Finland, a national screening program was launched as a randomised controlled trial in selected regions in 2004 (Paimela 2010). Between 2004 and 2006, people aged 60 to 64 years who were living in these areas were randomised 1:1 to screening with guaiac-based FOBT biennially or no screening; 52,998 people were included in the intervention group and 53,002 in the control group. The primary outcome is mortality from CRC and follow-up analyses are planned in 2014.

Risk of bias in included studies

See Characteristics of included studies and Figure 2. In general, the risk of bias was judged as low. In the Norwegian Telemark Polyp Study (TPS) (Thiis-Evensen 1999), risk of bias was rated as 'high' due to an inadequate randomisation procedure; in the intervention group, participants were drawn from the population registry among those born in January and February, while controls were randomised irrespective of month of birth. This introduced a potential selection bias. The TPS investigators indeed discovered a month-of-birth all-cause mortality difference, which confirms that a selection bias actually may have occurred (Hoff 1996). The remaining studies used adequate randomisation procedures. We did not detect any high risk of bias with respect to allocation concealment or blinding.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Blinding of participants was obviously not possible due to the nature of the interventions. Blinded verification of cause of death by independent experts who scrutinized the death certificates supplied with clinical information, when available, were performed in all trials except the two Norwegian trials.

All trials reported analyses by intention to treat. Loss to follow-up rates were 0.1% to 6.2%.

In three of the six regions in the Italian flexible sigmoidoscopy trial (Segnan 2011), participants were randomised on an individual or household basis. Cluster randomisation was applied in the other three regions with the general practitioner as the cluster unit. We contacted the principal investigator of the Italian trial (Segnan 2011) to obtain the intra-cluster correlation coefficient, but this was not calculated.

The Danish (Kronborg 2004), Swedish (Lindholm 2008) and English (Scholefield 2012) FOBT trials and the two Norwegian flexible sigmoidoscopy trials (Thiis-Evensen 1999; Hoff 2009) had a population-based design in which all, or a random sample of, age-eligible individuals were randomised to the intervention or the control group. In the US (Schoen 2012), British (Atkin 2010) and Italian (Segnan 2011) flexible sigmoidoscopy screening trials and in the US FOBT trial (Mandel 2000), individuals were recruited to participate in the trials from volunteers.

Effects of interventions

See: **Summary of findings for the main comparison** Screening for colorectal cancer with flexible sigmoidoscopy or faecal occult blood test

Colorectal cancer (CRC) mortality

See Analysis 1.1; Summary of findings for the main comparison; Summary of findings table 2. In the pairwise meta-analysis (random-effects model), the relative risk of mortality due to CRC was 0.86 (95% CI 0.80 to 0.92; four studies, N = 329,642) for FOBT compared to no screening (GRADE: high). The relative risk of CRC mortality was 0.72 (95% CI 0.65 to 0.79, five studies, N = 414,754) for flexible sigmoidoscopy compared to no screening (GRADE: high). There were no signs of significant heterogeneity between the trials (I^2 = 18% and 0% for the FOBT and flexible sigmoidoscopy comparisons, respectively). The risk of CRC mortality was reduced from 8 per 1000 across the control groups to 7 (95% CI 6 to 7) per 1000 with FOBT, and 6 (95% CI 5 to 6) per 1000 with sigmoidocopy.

In the multiple treatment meta-analysis (MTM), the relative risk (with 95% credibility interval (CrI)) of CRC mortality for flexible sigmoidoscopy compared to FOBT was 0.85 (95% CrI 0.72 to 1.01) (GRADE: low).

In the sensitivity analyses, we first excluded the trial with high risk of selection bias (Thiis-Evensen 1999). This did not alter our results. As the intra-cluster correlation coefficient was not reported in the Italian flexible sigmoidoscopy trial (Segnan 2011), this study was excluded in a sensitivity analysis as pre-specified in our protocol, without altering the results. When we limited the analysis and compared flexible sigmoidoscopy screening to biennial screening for faecal occult blood only (that is annual FOBT screening was excluded), the relative risk of dying due to CRC was 0.81 for flexible sigmoidoscopy screening compared to screening with FOBT (95% Crl 0.70 to 0.96) (GRADE: moderate).

In the US FOBT trial (Mandel 2000), 28% to 38% of participants had a colonoscopy during the trial compared to 4.4% to 8.8% in the other FOBT trials. When we excluded this trial from the MTM analysis asa post hoc sensitivity analysis, the relative risk for CRC mortality was 0.83 (95% Crl 0.70 to 0.99) when screening with flexible sigmoidoscopy was compared to FOBT.

Length of follow-up varied significantly between studies, ranging from a median of six years in the NORCCAP trial (Hoff 2009) to 19.5 years of follow-up in the English FOBT trial (Scholefield 2012). We therefore performed a sensitivity analysis (MTM) in which trials with approximately 10 years of follow-up were included; the Norwegian NORCCAP trial (Hoff 2009) was excluded due to the short follow-up (six years) leaving the British, Italian, US and Norwegian TPS trials eligible for analysis, with follow-up of approximately 11 to 13 years (Thiis-Evensen 1999; Atkin 2010; Segnan 2011; Schoen 2012). All FOBT trials were included, but we used the reports with follow-up as close to 10 years as possible, which were identical to the first reports of the CRC mortality and incidence of the trials (Mandel 1993; Hardcastle 1996; Kronborg 1996; Lindholm 2008). The relative risk for death due to CRC was 0.87 (95% Crl 0.73 to 1.05) for flexible sigmoidoscopy compared to FOBT.

Colorectal cancer incidence and staging

See Analysis 1.2; Summary of findings for the main comparison; Summary of findings table 2. The incidence of CRC was reduced by 18% in the flexible sigmoidoscopy trials, relative risk of 0.82 (95% CI 0.73 to 0.90; five studies, N = 414,744) in the random-effects model, but with substantial heterogeneity between the included studies (I^2 = 60%, P = 0.04, GRADE: moderate). The heterogeneity was 0% when the two Norwegian trials were removed from the analysis (Thiis-Evensen 1999; Hoff 2009). When FOBT was compared to no screening, the relative risk for CRC was 0.95 (95% CI 0.88 to 1.02). There was considerable heterogeneity between the trials (I^2 = 64%, P = 0.04, GRADE: moderate). The risk of CRC incidence was 20 per 1000 across the control groups. Corresponding estimates of CRC incidence were 19 per 1000 with FOBT (95% CI 18 to 20), and 16 per 1000 (95% CI 15 to 18) with flexible sigmoidocopy.

In the MTM analysis, the relative risk of CRC incidence with

flexible sigmoidoscopy compared to FOBT was 0.85 (95% CrI 0.72 to 1.02) (GRADE: low).

In the sensitivity analyses, the trial with high risk of bias (Thiis-Evensen 1999), the partly cluster randomised trial (Segnan 2011) and the short follow-up Norwegian trial (Hoff 2009) were excluded, and results in the MTM analyses were unchanged from the main analysis. When we excluded the US FOBT trial (Mandel 2000) trial, due to the very high colonoscopy rate in this study, the risk of being diagnosed with CRC was 18% lower if screening with flexible sigmoidoscopy was offered compared to FOBT (relative risk (RR) 0.82; 95% CrI 0.71 to 0.96). In the 10-year analysis, the CRC incidence was reduced by 21% when flexible sigmoidoscopy screening was compared to FOBT (RR 0.79; 95% CrI 0.70 to 0.90). In the analysis which only included biennial FOBT screening compared to flexible sigmoidoscopy, the results were similar to those in our main analysis (RR 0.82; 95% CrI 0.67 to 1.01).

The effect of screening on colorectal cancer staging was reported in all but the British trial. All showed a favourable shift towards less advanced tumours in the screening group, see Table 2.

All-cause mortality

See Analysis 1.3; Summary of findings for the main comparison; Summary of findings table 2. Mortality due to death from all causes was specifically reported for all trials but one of the Norwegian trials (Hoff 2009). The RR of death from all causes in the screening group was 0.98 (95% CI 0.95 to 1.01) compared to the control group in the flexible sigmoidoscopy trials, with moderate heterogeneity between the included studies (I^2 = 45%, P = 0.14, GRADE: high). Heterogeneity was 0% when the high risk of bias study from Norway was removed from the analysis (Thiis-Evensen 1999). For FOBT, the RR was 1.00 (95% CI 0.99 to 1.01) with no heterogeneity between trials (I^2 = 0%, GRADE: high). All-cause mortality was 254 per 1000 in the control groups. The corresponding risk of all-cause mortality was 254 (95% CI 251 to 257) per 1000 in the FOBT groups and 249 (95% CI 241 to 257) per 1000 in the sigmoidoscopy groups.

MTM revealed a RR of 0.98 (95% CrIs 0.95 to 1.00) for flexible sigmoidoscopy compared to FOBT (GRADE: moderate). Further sensitivity analyses, excluding studies with high risk of bias and studies with cluster design, did not change the results.

Attendance

See Table 1. Attendance rates were reported in all the included trials, but it was not possible to perform an indirect comparison due to different recruitment methods and reporting. At least one screening test was completed by 59% to 70% of participants in the population-based FOBT trials (Scholefield 2002; Kronborg 2004; Lindholm 2008), see Table 1. In the US trial (Mandel 2000), which recruited participants among screening volunteers, 90% of participants in both the annual and biennial screening groups completed at least one screening round. Attendance rates in the two population-based flexible sigmoidoscopy trials were 81% in the small Norwegian trial (Thiis-Evensen 1999) and 65% in the larger trial (Hoff 2009). The British (Atkin 2010), Italian (Segnan 2011) and US (Schoen 2012) sigmoidoscopy screening trials recruited participants from among those who had reported an interest in screening. Seventy-one per cent of those invited attended screening in the UK (Atkin 2010), 58% in Italy (Segnan 2011) and 87% in the US (Schoen 2012). In the UK trial (Atkin 2010), 194,726 of 368,142 (53%) eligible individuals responded with interest in screening, and 43,010 of 234,569 (18%) replied with 'certain' or 'probable' interest in screening in Italy (Segnan 2011). Thus, on the population level, attendance rates were 38% (0.71 x 0.53) and 10% (0.58 x 0.18) in the UK (Atkin 2010) and Italian (Segnan 2011) trials, respectively. In the US, the response to direct mailing varied between 0.3% and 3.4% for the 10 screening centres (Simpson 2000).

Adverse effects of screening

See Table 3. Physical adverse effects of the screening procedure and colonoscopy work-up were reported in all the flexible sigmoidoscopy trials, but only partly in the US trial (PLCO) (Schoen 2012). There was incomplete reporting of deaths related to the screening intervention or work-up colonoscopy and surgery. In the FOBT studies, physical adverse effects were due to colonoscopy work-up and surgical procedures after a positive screening test; they were specifically stated for all the trials except for the Danish trial (Kronborg 2004), and only partly in the US trial (Mandel 1993). A major complication (for example bleeding, perforation or death within 30 days of screening, follow-up colonoscopy or surgery) occurred in 0.03% and 0.08% of participants in the FOBT and flexible sigmoidoscopy trials, respectively.

Psychological effects of screening were addressed in the Italian (Segnan 2002), British (Taylor 2000; Miles 2003; Wardle 2003), two Norwegian (Hoff 2001; Larsen 2002; Larsen 2007), Swedish (Lindholm 1997), US PLCO (Schoen 2000) trials and the English FOBT trial (Parker 2002). Acceptance among screened persons was very high. Worry associated with the invitation or positive screening results, if present, was generally of short duration. Short-term effects on lifestyle and health attitudes were addressed in two reports from the British study (Miles 2003; Wardle 2003), and no negative effects were detected. Adverse effects on lifestyle were evaluated prospectively in a randomised controlled study within the NORCCAP trial (Larsen 2007). Three years after screening, attenders were more likely to gain weight and were less likely to stop smoking, engage in physical activity and eat fruit and vegetables compared to a randomly chosen sample from the control group. All these comparisons reached statistical significance.

Use of colonoscopy work-up

Due to disparities in the definition of a positive screening test, referral for colonoscopy varied accordingly. In the flexible sigmoidoscopy screening trials, referral rates for colonoscopy among screened persons were: 5.2% (2131/40,674), 8.4% (832/9911), 16.5% (17,672/107,236), 23% (2034/8846, combined FOBT and flexible sigmoidoscopy) and 34.6% (112/324) in the British (Atkin 2010), Italian (Segnan 2011), US (Schoen 2012), NORCCAP (Hoff 2009) and TPS (Thiis-Evensen 1999) trials, respectively. The US FOBT trial referred 28% of participants in the biennial screening group and 38% in the annual screening group for colonoscopy (Mandel 1993). Among attenders, screen-positive rates requiring work-up were: 8.8% (2108/23,916), 4.4% (1977/44,838) and 8.5% (1766/20,672) in the Swedish (Kewenter 1996), English (Hardcastle 1996) and Danish (Kronborg 2004) FOBT trials, respectively.

DISCUSSION

Summary of main results

There was high quality evidence from the pairwise meta-analysis that the risk of death from colorectal cancer (CRC) was reduced when faecal guaiac-based occult blood testing (14% reduction; 95% CI 8% to 20%) or flexible sigmoidoscopy (28% reduction; 95% CI 21% to 35%) were compared to no screening. The analyses were robust without heterogeneity between flexible sigmoidoscopy screening trials, and modest heterogeneity (I^2 = 18%, P = 0.3) between the results of thethe FOBT trials.

When we compared flexible sigmoidoscopy with faecal occult blood testing (FOBT) in the multiple-treatment meta-analysis (MTM), the estimated effect was a 15% reduction (95% CrI 1% increase to 28% reduction) in CRC mortality when screening with flexible sigmoidoscopy was compared to annual or biennial FOBT. In the MTM analysis, a 15% reduced incidence of cancer in colorectum was observed when screening with flexible sigmoidoscopy was compared to FOBT, but the credibility interval (CrI) crossed the value one, indicating that a difference between the screening tools might exist, but no difference cannot be ruled out. In addition, we rated this as low quality evidence, which means that we have little confidence in the effect estimate. The incidence of CRC was reduced by 18% in the flexible sigmoidoscopy trials (95% CI 26% to 10%). A reduction in the incidence of CRC by FOBT screening could not be established nor ruled out with a 5% reduction (95% CI 2% increase to 12% reduction).

With regard to all-cause mortality there was little or no difference between flexible sigmoidoscopy and FOBT(Relative risk 0.98; 95% CrI 0.95 to 1.00) using the MTM approach. The relative risk of death from all causes in the screening group was 0.98 (95% CI 0.95 to 1.01) compared to the control group in the flexible sigmoidoscopy trials. In the FOBT studies the relative risk was 1.00 (95% CI 0.99 to 1.01).

The rates of major complications in the flexible sigmoidoscopy groups was 8 in 10,000. Although headline rates of major complications were lower in the FOBT studies (3 in 10,000), this was associated with follow-up investigations, including sigmoidoscopy.

Overall completeness and applicability of evidence

As the sensitivity of the guaiac-based tests for detecting advanced adenomas is only 16% to 31% (van Dam 2010), no effect on CRC incidence was anticipated. This was indeed true for the Danish (Kronborg 2004), Swedish (Lindholm 2008) and English (Scholefield 2012) FOBT trials where the number of CRCs were almost identical in the screening and control groups. In the US FOBT trial (Mandel 2000), a statistically significant reduction in new cases of CRC was detected. This was most probably due to the very high rate of colonoscopies performed in this trial, 28% of attenders in the biennial screening group and 38% in the annual screening group. Colonoscopy rates were 4% to 9% in the other FOBT trials. We found a 5% decrease in CRC incidence when FOBT was compared to no screening, but heterogeneity was considerable among the trials. When we removed the US study from the analysis, heterogeneity was reduced to zero and no difference in CRC incidence between the control and screening groups could be detected.

In contrast to FOBT, flexible sigmoidoscopy has the ability to detect and remove precursor lesions from the examined part of the intestine. Our meta-analysis of the five flexible sigmoidoscopy trials showed a statistically significant reduction in new cases of CRC in the entire colon and rectum by 18%. There was considerable heterogeneity between these studies, which was mainly caused by the Norwegian NORCCAP trial (Hoff 2009). Removing this trial from the analyses revealed a heterogeneity of 18% (P = 0.3) in the comparison of the remaining trials. The NORCCAP trial (Hoff 2009) had a very short follow-up (six to seven years) compared to the other trials (11 to 13 years) and this may be the reason for the heterogeneity. Other reasons, like differences in study design, cannot be ruled out however.

One reason why a difference in the incidence of cancer in the colorectum between FOBT and flexible sigmoidoscopy could not be established could be the high colonoscopy rate in the US FOBT trial (Mandel 2000). It has been argued that the reduction in incidence in this study may have been due to chance and caused by the poor specificity of the rehydrated FOBT test used, and not by a high test sensitivity (Lang 1994), thus the rehydrating guaiac-based FOBT test is no longer recommended (Levin 2008). This motivated us to perform the sensitivity analysis in which this study was excluded, showing a 18% reduction in incidence in favour of

flexible sigmoidoscopy screening compared with FOBT (95% CrI 0.71 to 0.96).

In recent years, evidence of a different biology between proximal and distal CRC has been proposed (Gervaz 2004), and this may have implications for screening. The effect of screening on mortality from proximal versus distal CRC was reported in the Danish and English FOBT trials. No statistically significant differences in protection from right- or left-sided CRC deaths were found, although there was a trend towards a greater reduction in mortality from proximal compared to distal colon cancers. Among the flexible sigmoidoscopy trials, the Italian (Segnan 2011) and US (Schoen 2012) trials specifically reported an effect of screening on CRC mortality from right- compared to left-sided CRC. In neither of the trials was mortality from right-sided CRC reduced. The evidence supports the idea of combining the two screening modalities and this issue has been addressed in a number of trials (Berry 1997; Rasmussen 1999; Denis 2009). These studies indicate that adding flexible sigmoidoscopy to FOBT substantially reduces compliance with screening, but is counter-balanced by a three to seven times higher diagnostic yield of advanced adenomas despite the lower compliance. Whether the higher rate of advanced adenoma detection and subsequent removal and surveillance translates into lower mortality or incidence of CRC is unknown.

Prior case-control studies have anticipated that endoscopic examination and polypectomy in the distal colon may reduce CRC incidence in this area by 70% to 80% (Atkin 1992; Selby 1992; Newcomb 2003), but with no reduction in the incidence of CRC located proximal to the sigmoid colon (Newcomb 2003). Incidence rates for proximal and distal CRC in the British and Italian trials support these findings. CRC incidence was reduced by 36% and 24% in the distal colon, but only by a non-significant 2% and 9% in the proximal colon in the two trials, respectively. In the PLCO trial, on the other hand, the CRC incidence was reduced in both the distal colon, by 29%, and the proximal colon, by 14% (both $P < 0.05$). The anticipated lack of effect on mortality and incidence of right sided colon cancers by flexible sigmoidoscopy has made colonoscopy a gold standard in screening for CRC, despite no evidence of efficacy from prospective trials. Recently, two case-control studies have questioned the role of colonoscopy role in preventing right-sided CRC. Prior exposure to colonoscopy was associated with reduced mortality from distal but not proximal CRC in a study from Canada (Baxter 2009), and reduced incidence of left-sided but not right-sided advanced adenomas was evident in a report from Germany (Brenner 2010. A third case-control study from the latter group provided conflicting evidence to the former two, showing a relative risk of 0.44 (95% CI 0.35 to 0.55) for developing proximal CRC in 1688 cases who had had a colonoscopy in the preceding 10 years compared to 1932 matched controls who were unexposed to colonoscopy in the same time period (Brenner 2011).

When comparing flexible sigmoidoscopy and FOBT, time to follow-up becomes a highly relevant and complex issue. FOBT reduces CRC specific mortality by detecting early stage disease with a favourable prognosis, but new cases (incidence) are not reduced as the sensitivity for precursor lesions is low. This means that after FOBT screening has come to an end, new cases of CRC will develop with the same rate in those previously screened as in the control group. Thus, the protective effect of the screening intervention is no longer present, or at least to a lesser extent, after screening has ceased. This is well demonstrated by the three reports from the English FOBT trial, where screening stopped in February 1995. The first report had a cut-off for follow-up three months after the end of screening (Hardcastle 1996), the second at four years (Scholefield 2002) and the third 14 years after screening had ceased (Scholefield 2012). The reduction in CRC mortality in favour of the screening group was 15% (95% CI 2% to 26%), 13% (95% CI 3% to 22%) and 9% (95% CI 2% to 16%) in the three reports, respectively. The effect of flexible sigmoidoscopy, on the other hand, seems to be long lasting. After a median of approximately 11 years in the British (Atkin 2010), Italian (Segnan 2011) and US (Schoen 2012) flexible sigmoidoscopy screening trials, survival curves of the screening group and control group are still diverging, indicating that the maximum effect of flexible sigmoidoscopy screening has not yet been achieved, and that the mortality rate ratios are still in favour of the screening group (Atkin 2010). Thus, choosing only the last report from the trials in the MTM analysis, as pre-specified in our protocol, may not provide the right answer. The 10-year sensitivity analysis included the first reports after FOBT screening had stopped and should thus include the maximum effect of the FOBT screening intervention. In addition, times to follow-up are more similar in the flexible sigmoidoscopy trials. In this analysis, the incidence of CRC was reduced when flexible sigmoidoscopy screening was compared to FOBT, while there was a trend towards reduced mortality from CRC when flexible sigmoidoscopy screening was compared to FOBT; the credibility interval of the latter analysis just crossed 1.

When policymakers consider the implementation of a screening program for colorectal cancer, they should base their judgement on high-quality evidence that is applicable to their population and setting. Much of the evidence in this review is of high quality, but the applicability of the findings to a real-life screening programme may be questioned due to how some of the studies were designed. The only true population-based trials mimicking a screening programme are the English FOBT trial (Scholefield 2002) and the Norwegian NORCCAP study (Hoff 2009). All other trials applied study designs which impair applicability. The two US trials, (Schoen 2012; Mandel 1993), the British (Atkin 2010) and Italian (Segnan 2011) trials recruited volunteers to participate in the studies. This design increases statistical power, but the effect on the population level may be overestimated. In Denmark (Kronborg 2004), only those participating in the preceding screening round were invited for the next, which may underesti-

mate the screening effect on the population level. The three cohorts in the Swedish trial (Lindholm 2008) were offered only a limited number of screening rounds with FOBT, and the small Norwegian TPS study (Thiis-Evensen 1999) suffered from a potentially biased randomisation sequence procedure. Thus, results from the individual studies should be interpreted with these points in mind.

We did not detect any reduction in all-cause mortality for either screening test. This is an expected finding as CRC is a quite rare cause of death. To show an effect of CRC screening on all-cause mortality, a very large number of individuals would have to be included, and the present studies are underpowered to detect a difference regarding this endpoint.

An evaluation of costs of screening was beyond the scope of this review. Many cost-benefit analyses have been performed in the CRC screening setting. Neither flexible sigmoidoscopy nor FOBT has been proven to be superior to the other. In addition, these analyses are based on numerous assumptions, which may differ substantially between countries and make it not possible to generalize results across the borders (Lansdorp-Vogelaar 2010).

Potential biases in the review process

The MTM is based on the use of both indirect and direct evidence for estimation of the difference between two interventions (in this review: screening methods). In our specific case, we did not find any head-to-head comparisons of flexible sigmoidoscopy versus faecal occult blood testing (FOBT). As a consequence, the results regarding this comparison are based on indirect evidence only. The validity of our results for the comparison of flexible sigmoidoscopy versus FOBT thus depends heavily on the assumption that the common comparator (no screening) arms in the included studies are sufficiently similar. Data were scarce in the included studies regarding important demographic variables such as ethnicity, smoking history, level of education and physical activity. To judge comparability, we scrutinized the exclusion criteria in the individual studies and the incidence and mortality rates in the control groups, see Characteristics of included studies, Table 4, Table 5. Even if some differences exist, we think that these do not undermine our assumption of comparability, but with no direct evidence for the flexible sigmoidoscopy versus FOBT comparison it is impossible for us to quantity the inconsistency in the system. One should also be aware of the fact that our analyses are by intention to treat. This means that we compared screening programmes including flexible sigmoidoscopy or FOBT and not the screening modalities as such. In other words, we assessed the impact of screening at the population level, which takes into account the degree to which individuals choose to attend screening or not. The effect of screening among those who decided to take part in the programme ('efficacy') may be different than our effect estimates.

AUTHORS' CONCLUSIONS

Implications for practice

There is high quality evidence that screening by guaiac-based FOBT and flexible sigmoidoscopy both reduce mortality due to colorectal cancer. Neither FOBT nor flexible sigmoidoscopy was shown to reduce all-cause mortality. We are unable to draw definitive conclusions with regard to the frequency or severity of physical adverse events attributable to screening due to incomplete reporting of these data. Flexible sigmoidoscopy reduces CRC incidence while the results for FOBT are inconclusive

In the absence of direct evidence comparing the two screening approaches, we are not certain as to whether one screening tool reduces colorectal cancer deaths more than the other. There was low quality evidence of a lower rate of CRC mortality associated with flexible sigmoidoscopy. The evidence underlying our estimates is too weak to draw any definitive conclusion about the relative effectiveness of the two screening methods. .

The effectiveness of a screening programme is heavily dependent on adherence to screening and should be assessed in pilot studies prior to implementation of a screening programme, as the population's acceptance of the screening modality may vary among different countries (Segnan 2005; Hol 2010). Available resources, both financial and human, also have to be considered. Cost-benefit analyses have to be performed in the context of each country, as assumptions in such analyses may differ substantially between countries and make conclusions non-generalizable (Lansdorp-Vogelaar 2010).

Implications for research

A number of research questions remain to be answered. We do not know the optimal age for screening and whether this differs between screening modalities. A colonoscopy screening study from Poland suggests that the diagnostic yield of advanced adenomas differs with sex and age, and different screening strategies may be warranted for men and women (Regula 2006). Guaiac-based FOBTs are the only FOBTs with proven effectiveness on CRC mortality. Immunologic FOBTs (FIT) have higher sensitivity for CRC (61% to 91%) and advanced neoplasia (27% to 67%) than the guaiac-based tests (25% to 38% and 16% to 31%, respectively) and have only slightly lower specificity (91% to 98% versus 98% to 99%, respectively) (van Dam 2010). The test procedure with FIT is also more convenient for the person to be screened, who only has to provide faeces from one passage of stool instead of two samples from three consecutive days, and no dietary restrictions are necessary. These advantages have been shown to increase adherence to screening and the diagnostic yield of advanced adenomas (Hol 2010), but repeated FIT has to our knowledge never been evaluated with respect to CRC mortality. It would be of great interest to compare FIT to flexible sigmoidoscopy in a randomised trial with mortality from CRC as the outcome. The

possible 'health certificate effect' (Stewart-Brown 1997) among screened persons indicated in the NORCCAP trial may have an important impact if screening is introduced in the population and should be addressed in future studies (Larsen 2007). Ascertainment and reporting of adverse events is an important priority for future research in this area.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Atkin 2002

Methods	See Atkin 2010 Patient satisfaction assessed by questionnaire completed at baseline (the day after the flexible sigmoidoscopy) and after 3 months
Participants	See Atkin 2010
Interventions	See Atkin 2010
Outcomes	Physical complications due to screening by flexible sigmoidoscopy and colonoscopy work-up Patient satisfaction with the screening procedure
Notes	Numbers of individuals assigned to screening and control group differs from Atkin 2010

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Atkin 2010
Allocation concealment (selection bias)	Low risk	See Atkin 2010
Blinding (performance bias and detection bias) All outcomes	Low risk	See Atkin 2010
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline questionnaire complete in 98% of screened persons Follow-up questionnaire complete in 91% of screened persons
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Atkin 2010

Methods	574 general practices around 14 screening-centres in the UK were invited to participate, and 506 practices accepted the invitation. Recruitment and screening was performed November 1994 - March 1999. All eligible individuals in the participating general practices were screened for predefined exclusion criteria by their general practitioner, and the remaining received an information letter and questionnaire to establish interest in screening. Those who reported interest in screening were randomly assigned to the screening or control group in the ratio 1:2, respectively, by a central randomisation unit in blocks of 12. Randomisation was stratified according to household, trial centre and general practice. Persons in the control group were not contacted further. Follow-up was by public registries. At follow-up after median 11.2 years, six people in either group could not be traced. A further 234 persons in the screening group and 451 in the control group had emigrated
Participants	Individuals aged 55 - 64 who responded with interest in screening and who did not meet any exclusion criteria: history of CRC, adenomas or inflammatory bowel disease; inability to provide informed consent; severe or terminal disease; life expectancy less than 5 years; sigmoidoscopy or colonoscopy within the previous 3 years. Persons reporting a strong family history of CRC or symptoms of CRC were also excluded and managed outside the trial
Interventions	Flexible sigmoidoscopy once only with removal of small polyps and referring for full colonoscopy if they had polyps 10 mm or larger, three or more adenomas, adenomas with tubulovillous or villous histology, severe dysplasia or malignant disease, or 20 or more hyperplastic polyps above the distal rectum
Outcomes	Compliance with screening, number referred for colonoscopy work-up, incidence of CRC (total, proximal and distal), yearly hazard rate, number needed to screen to prevent one colorectal cancer, all-cause mortality, mortality from CRC (intention-to-treat and per protocol), number needed to screen to prevent one death due to CRC
Notes	Compliance to screening reported as 71% (40674/57237) in the screening population. On the population-level, compliance will be lower due to the two-step invitation procedure

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequentially numbered randomisation was done centrally in blocks of 12 and with the added constraint of no more than three consecutive allocations to one group within or across blocks
Allocation concealment (selection bias)	Low risk	Central randomisation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcomes were obtained from or confirmed by public registries. A second analysis as CRCas an underlying cause of death

Atkin 2010 (*Continued*)

		was obtained after blinded verification of death certificates by an independent expert coder who had access to clinical information when available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six people in each group could not be traced. 658 people had emigrated
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported on
Other bias	Low risk	No other threats to validity detected

Gondal 2003

Methods	See Hoff 2009
Participants	Individuals aged 50-64 living in city of Oslo and Telemark county, Norway
Interventions	See Hoff 2009
Outcomes	Physical complications from screening with flexible sigmoidoscopy and colonoscopy work-up
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Hoff 2009
Allocation concealment (selection bias)	Low risk	See Hoff 2009
Blinding (performance bias and detection bias) All outcomes	Low risk	See Hoff 2009
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Hoff 2009
Selective reporting (reporting bias)	Low risk	See Hoff 2009
Other bias	Low risk	See Hoff 2009

Hardcastle 1996

Methods	See Scholefield 2012. Median follow-up 7.8 years	
Participants	See Scholefield 2002	
Interventions	See Scholefield 2002	
Outcomes	CRC mortality, CRC incidence, staging	
Notes	Number of people included in analyses differ from those reported in Scholefield 2002 and Scholefield 2012	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Scholefield 2002
Allocation concealment (selection bias)	Low risk	See Scholefield 2002
Blinding (performance bias and detection bias) All outcomes	Low risk	See Scholefield 2002
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Scholefield 2002
Selective reporting (reporting bias)	Low risk	See Scholefield 2002
Other bias	Low risk	See Scholefield 2002

Hoff 1996

Methods	See Thiis-Evensen 1999. Follow-up 10 years after screening	
Participants	See Thiis-Evensen 1999	
Interventions	See Thiis-Evensen 1999	
Outcomes	CRC mortality, CRC incidence, all-cause mortality	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Hoff 1996 (*Continued*)

Random sequence generation (selection bias)	High risk	See Thiis-Evensen 1999
Allocation concealment (selection bias)	Low risk	See Thiis-Evensen 1999
Blinding (performance bias and detection bias) All outcomes	Low risk	See Thiis-Evensen 1999
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Thiis-Evensen 1999
Selective reporting (reporting bias)	Low risk	See Thiis-Evensen 1999
Other bias	Low risk	See Thiis-Evensen 1999

Hoff 2001

Methods	See Thiis-Evensen 1999. Body Mass Index (BMI) and smoking habits were assessed in attenders at baseline flexible sigmoidoscopy screening in 1983 and at follow-up after 13 years. Participants were compared according to the findings at screening (any polyp versus no polyps detected). Data were available for all but 3 individuals
Participants	See Thiis-Evensen 1999
Interventions	See Thiis-Evensen 1999
Outcomes	BMI, smoking habits, all-cause mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable

Hoff 2001 (*Continued*)

Other bias	Unclear risk	Not applicable

Hoff 2009

Methods	Eligible participants were individually randomised centrally to the screening group or control group between January 1999 and December 2000. In the screening group, there was a further 1:1 randomisation to either flexible sigmoidoscopy only or FOBT combined with flexible sigmoidoscopy. 459 people allocated to the screening group were excluded from the screening procedure, but included in the intention-to-screen analyses, due to pre-specified exclusion criteria. Follow-up was purely registry based and participants in the control group were never contacted. Finally, 1196 people were lost to follow-up due to emigration and 21 people were censored as a result of colorectal malignancy other than colorectal adenocarcinoma. CRC mortality was reported after median 6 years and CRC incidence after median 7 years
Participants	All residents aged 55-64 living in the city of Oslo and Telemark County, Norway by November 1998. Individuals with a history of CRC were excluded
Interventions	Flexible sigmoidoscopy once only or flexible sigmoidoscopy combined with immunologic FOBT. During the endoscopic screening procedure, all detected lesions were biopsied. A positive screening test qualifying for full colonoscopy work-up and polypectomy was defined as any polyp 10 mm or more in diameter, any histologically verified adenoma irrespective of size, carcinoma or a positive FOBT
Outcomes	Incidence of CRC, incidence of rectosigmoid CRC, incidence of neoplastic lesions, incidence of high-risk adenomas, mortality from CRC, mortality from all causes, stage of CRC, compliance with screening, rate and compliance of colonoscopy work-up
Notes	In 2000, the trial was expanded for one year (throughout 2001) including persons aged 50-54 and randomised in the same way as those previously enrolled. This group is not reported on in this paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done independently according to social security number by the National Bureau of Statistics
Allocation concealment (selection bias)	Low risk	Central randomisation process
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcomes were obtained from public registries by a person not involved in the trial

Hoff 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	1196 people were lost to follow-up due to emigration
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Jorgensen 2002

Methods	See Kronborg 2004. Follow-up 13 years after commencement of screening
Participants	See Kronborg 2004
Interventions	See Kronborg 2004
Outcomes	CRC incidence, CRC mortality, all-cause mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Kronborg 2004
Allocation concealment (selection bias)	Low risk	See Kronborg 2004
Blinding (performance bias and detection bias) All outcomes	Low risk	See Kronborg 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Kronborg 2004
Selective reporting (reporting bias)	Low risk	See Kronborg 2004
Other bias	Low risk	See Kronborg 2004

Kewenter 1994

Methods	See Lindholm 2008. Follow-up 2-7 years after end of the pre-screening
Participants	See Lindholm 2008
Interventions	See Lindholm 2008

Kewenter 1994 (*Continued*)

Outcomes	CRC incidence, staging	
Notes	CRC mortality not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Linndholm 2008
Allocation concealment (selection bias)	Low risk	See Linndholm 2008
Blinding (performance bias and detection bias) All outcomes	Low risk	See Linndholm 2008
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Linndholm 2008
Selective reporting (reporting bias)	Low risk	See Linndholm 2008
Other bias	Low risk	See Linndholm 2008

Kewenter 1996

Methods	See Lindholm 2008. This report addresses endoscopic and surgical complications of work-up after a positive FOB screening test	
Participants	See Lindholm 2008	
Interventions	See Lindholm 2008	
Outcomes	Physical complications due to FOBT screening	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable

Kewenter 1996 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Kronborg 1996

Methods	See Kronborg 2004. 10 years follow-up after start of screening
Participants	See Kronborg 2004
Interventions	See Kronborg 2004
Outcomes	CRC incidence, CRC mortality, all-cause mortality, staging
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Kronborg 2004
Allocation concealment (selection bias)	Low risk	See Kronborg 2004
Blinding (performance bias and detection bias) All outcomes	Low risk	See Kronborg 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Kronborg 2004
Selective reporting (reporting bias)	Low risk	See Kronborg 2004
Other bias	Low risk	See Kronborg 2004

Kronborg 2004

Methods	Eligible persons were randomised centrally by block-randomisation of 14 to the intervention group, control group or not enrolled. Married couples were always randomised to the same group. Controls were never contacted. Follow-up was based on public registries. Only people participating in the preceding screening round were invited for the next round. Screening started in August 1985 and ended in August 2002. No participants were lost to follow-up 17 years after study start
Participants	Subjects aged 45 - 75 years living in Funen, Denmark, in 1985. Exclusion criteria: People with a history of CRC, adenomas, distant spread from all types of malignant disorders or participants in the pilot study preceding the trial
Interventions	Guaiac-based FOBT with dietary restrictions every second year. The slides were not rehydrated. A positive screening test was defined as one or more blue slides out of six and qualified for work-up with colonoscopy
Outcomes	Incidence of CRC, mortality from CRC by intention-to-treat and per protocol, stage of CRC, mortality from all causes, compliance with screening and work-up
Notes	Separate analysis of CRC mortality which included death due to treatment of CRC (postoperative complications)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central block randomisation procedure based on social security number
Allocation concealment (selection bias)	Low risk	Central randomisation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	The investigators were unaware of the trial allocation during the assessment of death certificates
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed until death or end of study
Selective reporting (reporting bias)	Low risk	All relevant outcome were reported
Other bias	Low risk	No other threats to validity detected

Larsen 2002

Methods	See Hoff 2009 Individuals attending screening with flexible sigmoidoscopy between January 1999 and February 2000 were given a questionnaire immediately after the examination to be filled in and returned by mail the following day
Participants	Individuals aged 55-64 who attended screening with flexible sigmoidoscopy
Interventions	Questionnaire filled in by participants in a flexible sigmoidoscopy screening trial
Outcomes	Participants' satisfaction
Notes	Not randomised study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Hoff 2009. This substudy was not randomised as all screened persons attending the trial between January 1999 and February 2000 were included

Larsen 2007

Methods	See Hoff 2009 Individuals randomised to screening with flexible sigmoidoscopy or to the control group received questionnaires on selected lifestyle indicators at baseline and after 3 years
Participants	People aged 50-55 in Telemark County and city of Oslo. Exclusion criteria: history of CRC
Interventions	Questionnaire filled in by individuals randomised to screening with flexible sigmoidoscopy or to a control group
Outcomes	Selected lifestyle indicators
Notes	Analyses not by intention to treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Hoff 2009
Allocation concealment (selection bias)	Low risk	See Hoff 2009

Larsen 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Handling and blinding of questionnaires not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individuals lost to follow-up and proportion of non-responders quite similar in the two groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	No other threats to validity detected

Lindholm 1997

Methods	See Lindholm 2008. All individuals in the cohort included in 1990 and 1991 and who were randomised to the intervention group received a questionnaire two weeks after the invitation to screening. A sample of these individuals were also chosen for a combined structured/open interview by telephone or personal meeting according to the test results or non-attendance
Participants	Individuals aged 60-64 in Gothenburg, Sweden, who were invited to screening with FOBT
Interventions	Mailed questionnaire received 2 weeks after invitation to screening with FOBT and combined structured/open interview at different occasions according to test results
Outcomes	Worry and interference with daily activities caused by invitation to or results of screening Patient satisfaction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable

Lindholm 1997 (*Continued*)

Other bias	Unclear risk	Not applicable

Lindholm 2008

Methods	Participants were invited for screening on 2-3 occasions in 3 cohorts. All 3 cohorts had their own screening scheme. Cohort 1 (recruited August 1982 - June 1983) had rescreening after 21-24 months and after approximately 11 years. Cohort 2 (recruited January 1987 - March 1988) had one rescreening after 21-24 months, and cohort 3 (recruited January 1990 - November 1990) had rescreening one and two years after the prevalent screen. Until 1984, a positive screening-test qualifying for follow-up was defined as one positive test-slide out of six. After 1984, those with positive test was re-tested with FOBT, and only those with at least one positive test slide out of six the second time were referred for work-up. The work-up investigation consisted of a flexible sigmoidoscopy and a double-contrast barium enema. 532 individuals lost to follow-up due to emigration. Participants were followed through public registries for a median of 15 years and 6 months
Participants	All inhabitants aged 60-64 living in Gothenburg, Sweden. Individuals with a history of CRC were excluded
Interventions	Guaiac-based FOBT with dietary restrictions. Two samples from 3 consecutive stools were collected. FOBT from the first half of cohort 1 was not rehydrated, but all later tests in this cohort and all FOBT in cohort 2 and 3 were rehydrated
Outcomes	Incidence of CRC, death from CRC and all causes by intention-to-screen and per protocol analyses, CRC staging, compliance, diagnostic work-up
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described
Allocation concealment (selection bias)	Low risk	Central randomisation procedure based on the population registry
Blinding (performance bias and detection bias) All outcomes	Low risk	CRC diagnosis and cause of death obtained from public registries. In cases of uncertainty of cause of death, an independent reviewer who was blinded to study group allocation evaluated case records
Incomplete outcome data (attrition bias) All outcomes	Low risk	All individuals could be traced at follow-up except for 532 emigrants

Lindholm 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Mandel 1993

Methods	Eligible individuals were randomly allocated to screening with FOBT (annually or biennially) or to a control group who were not offered any screening. Participants were stratified according to sex, age and place of residence prior to randomisation. Screening started in 1976 and ended in 1982. In February 1986, screening was resumed due to lower than expected mortality from CRC in the control group. This second screening period ended in February 1992. All death certificates along with medical records were reviewed by a blinded review committee. A study pathologist staged all slides from patients with a diagnosis of CRC. All participants in the screening- and control groups were mailed a questionnaire annually to ascertain their vital status and occurrence of CRC and polyps. Follow-up was for 13 years
Participants	People aged 50-80 years recruited among volunteers for the American Cancer Society and fraternal, veterans, and employee groups in Minnesota, USA. Exclusion criteria: People with a history of CRC, familial polyposis, chronic ulcerative colitis and persons known to be bedridden or otherwise disabled
Interventions	Guaiac-based FOBT with dietary restrictions. Two samples from three consecutive stools were obtained. 82.5% of the test slides were rehydrated. A positive screening test was defined as one or more blue test slides out of six and qualified for work-up which included colonoscopy
Outcomes	Compliance with screening, complications due to colonoscopy work-up, incidence of CRC, mortality from CRC, all-cause mortality, stage of CRC
Notes	Colonoscopy performed in 38% of participants in the annual screening group, and in 28% of participants in the biennial screening group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Weekly randomisation as participants were enrolled after stratification for age, sex and place of residence
Allocation concealment (selection bias)	Low risk	Participants stratified and placed in groups of three who were subsequently randomised to one of six permutations which allocated the three participants to either of the three study groups

Mandel 1993 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Outcomes assessed by a death review committee and a study pathologist who were unaware of study allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Death certificates obtained for 99.9% of participants
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	Participants recruited among volunteers

Mandel 1999

Methods	See Mandel 1993 Vital status complete for 88.8%, 89.1% and 88.5% and death certificates were obtained for 99.7%, 99.8% and 99.8% for annual, biennial and control group participants, respectively. Follow-up was for 18 years
Participants	See Mandel 1993
Interventions	See Mandel 1993
Outcomes	All-cause mortality, mortality from CRC
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Mandel 1993
Allocation concealment (selection bias)	Low risk	See Mandel 1993
Blinding (performance bias and detection bias) All outcomes	Low risk	See Mandel 1993
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Mandel 1993
Selective reporting (reporting bias)	Low risk	See Mandel 1993
Other bias	Low risk	See Mandel 1993

Mandel 2000

Methods	See Mandel 1993. Follow-up for 18 years
Participants	See Mandel 1993
Interventions	See Mandel 1993
Outcomes	Incidence of CRC
Notes	See Mandel 1993

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Mandel 1993
Allocation concealment (selection bias)	Low risk	See Mandel 1993
Blinding (performance bias and detection bias) All outcomes	Low risk	See Mandel 1993
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Mandel 1993
Selective reporting (reporting bias)	Low risk	See Mandel 1993
Other bias	Low risk	See Mandel 1993

Miles 2003

Methods	See Atkin 2010 A sample of individuals invited for screening was included. Individuals were divided into three groups and compared according to the outcome from the flexible sigmoidoscopy screen: 1) Individuals with a negative screening result (no significant pathology), 2) individuals with a low-risk result (1-2 adenomas 9 mm or less with a tubular histology and mild to moderate dysplasia or less than 20 hyperplastic polyps) and 3) individuals with a high-risk result (3 or more adenomas, adenoma 10 mm or larger, adenoma with tubulovillous or villous histology or severe dysplasia or 20 or more hyperplastic polyps) who were recommended colonoscopy work-up
Participants	People aged 55-64 in three selected screening areas in the UK
Interventions	Questionnaire about health attitudes and selected lifestyle indicators before screening with flexible sigmoidoscopy and 3 months post-screening
Outcomes	Selected health attitudes and lifestyle indicators

Miles 2003 (*Continued*)

Notes	Main analysis not by intention-to-treat, but sensitivity analyses by intention-to-treat did not change results of the main analysis. There was no no-screening control group. The no-risk and low-risk group only had flexible sigmoidoscopy, while the high-risk group had both flexible sigmoidoscopy and full colonoscopy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Parker 2002

Methods	See Hardcastle 1996 2184 individuals assigned to the screening group were randomly chosen to received a questionnaire (the General Health Questionnaire) by mail before the offer of screening and 3 months after screening to asses psychiatric morbidity. Participants were recruited from two general practices. The participants returned the questionnaire by mail. 1693 (70.6%) of the individuals returned the first questionnaire. Of the 1693 subjects offered the questionnaire 3 months after screening,1303 (77%) completed the form. Anxiety levels were measured by another self-administered questionnaire in all subjects with a positive FOBT. This questionnaire was completed each time the participant attended the hospital, the day after each visit and 1 month after the results of the investigations were known. Data from 100 persons with a false positive FOBT was analysed
Participants	A sample of participants aged 50 to 75 allocated to screening with FOBT
Interventions	1): Questionnaire before screening and 3 months after screening with FOBT 2): Questionnaire at each hospital visit, the day after the hospital visit and 1 month after the result of the colonoscopy work-up examination in participants with a positive FOBT
Outcomes	Psychiatric adverse effects of screening with FOBT

Parker 2002 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Robinson 1999

Methods	See Scholefield 2002. This report mainly addresses complications due to work-up after positive FOB screening tests
Participants	See Scholefield 2002
Interventions	See Scholefield 2002
Outcomes	Physical complications related to screening with FOBT
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable

Robinson 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Schoen 2000

Methods	A total of 1221 individuals (of whom 97% was participating in the PLCO trial) at two screening centre were recruited. A questionnaire was completed on site immediately after the screening intervention or returned by mail a few days after the examination. A random sample completed 2 open-ended questions about the screening experience and their expectations
Participants	Ninety-seven per cent participated in the PLCO trial
Interventions	Questionnaire
Outcomes	Convenience and accessibility, staff interpersonal skills, physical surroundings, perceived technical competence, expectations and beliefs, general satisfaction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Schoen 2012

Methods	Eligilbe individuals were invited to participate in the trial by mass mailing. People who reported interest in screening provided written informed consent and completed a baseline questionnaire before randomisation which was performed in blocks stratified according to screening centre, age and sex. A total of 154,900 people were enrolled from 1993 through 2001; 77,445 to the intervention group and 77,455 to the control group. All cancers and deaths were primarily assessed through a annually mailed questionnaire to all participants and subsequently verified from medical records and through linkage to public registries. Deaths that were potentially related to colorectal cancer were reviewed in a blinded fashion. CRC deaths included deaths due to CRC and its treatment
Participants	Individuals 55 to 74 years of age with no prior history of prostate, lung, colorectal or ovarian cancer. Other exclusion criteria were: ongoing treatment of any type of cancer except basal-cell or squamous-cell skin cancer and, beginning in 1996, flexible sigmoidoscopy, colonoscopy or barium enema in the previous 3 years
Interventions	Participants in the intervention group were offered a flexible sigmoidoscopy at baseline and at 3-5 years. Participants in the control group were not offered any screening and continued to receive "care as usual". The screening interventions were conducted at ten screening centres. A positive test result was defined as a finding of a polyp or a mass. Biopsies were not routinely performed, but individuals with a positive test were referred to their general practitioner for decisions regarding diagnostic follow-up
Outcomes	CRC mortality, CRC incidence, all-cause mortality, staging, physical complications due to screening and follow-up colonoscopy
Notes	Carcinoid tumours were included as colorectal cancers 46.5% of participants in the control group had a flexible sigmoidoscopy or colonoscopy during the screening phase of the study. The rate of routine colonoscopy after the screening phase was 47.7% in the intervention group and 48.0% in the control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Volunteers who responded to an invitation through mass-mailing were randomised using a central block-randomisation process stratified according to screening centre, age and gender
Allocation concealment (selection bias)	Low risk	Central randomisation process
Blinding (performance bias and detection bias) All outcomes	Low risk	Death review group unaware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Vital status was known for 99.9% of participants, and compliance with the annual study update questionnaire was 93.8%

Schoen 2012 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No reports of adverse effects due to colonoscopy follow-up
Other bias	Low risk	No other threats to validity detected

Scholefield 2002

Methods	See Scholefield 2012. Median follow-up 11.7 years
Participants	See Scholefield 2012
Interventions	See Scholefield 2012
Outcomes	Incidence of CRC, CRC mortality, all cause mortality, number of positive screening tests, work-up, compliance with screening
Notes	Number of people included in the analyses differ from the previous report of this trial (Hardcastle 1996)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation process by household. More than 50% of households were single persons
Allocation concealment (selection bias)	Low risk	Central randomisation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Study investigators who assessed cause of death and pathologists were unaware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	547 persons could not be traced or had emigrated
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Scholefield 2012

Methods	Eligible individuals were recruited to the study between February 1981 and June 1983 (pilot study) and February 1985 and January 1991 (main study). People were identified according to the general practice at which they were registered. Family doctors at each practice were asked to exclude any person with serious illness including a diagnosis of CRC the previous 5 years. Randomisation was by household and stratified according to size, sex and average age of eligible members within the household. Housholds were randomly allocated to screening with FOBT or no screening. After randomisation, 547 people could not be traced and were excluded from the mortality analysis. Persons in the control group were not contacted. Follow-up was based on public registries, histopathologic registers at the local hospitals and family doctors' reports. Strutured case note reviews of certified and registered CRC cases were carried out in order to verify cause of death. Median follow-up was 19.5 years
Participants	People aged 45-75 living in the Nottingham area of the UK
Interventions	Guaiac based FOBT every second year. Two samples of three consecutive stools were collected. The test was taken without dietary restrictions and without rehydration of the test slides. In the pilot study, a positive screening test was defined as one or more blue test slides and individuals with a positive test were referred for flexible sigmoidoscopy and double contrast enema. In the main study, a positive screening test was defined as five or six blue test slides, and these persons were referred for colonoscopy. Individuals with 1-4 positive test slides in the initial screening test were retested with the FOBT. Dietary restrictions were applied, and two samples from six consecutive stools were collected. Those with one or more positive test slides in the retest were offered colonoscopy. Screening participants with a negative retest were asked to repeat the test again with dietary restrictions after 3 months and were offered colonoscopy if they tested positive
Outcomes	Incidence of CRC, mortality from CRC, all-cause mortality
Notes	People excluded from analyses due to emigration or other causes different from the other reports from the same study; Hardcastle 1996 and Scholefield 2002

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation process by household. More than 50% of households were single persons
Allocation concealment (selection bias)	Low risk	Central randomisation procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Study investigators who assessed cause of death and pathologists were unaware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	875 people could not be traced or had emigrated after randomisation and were excluded from analyses. Not stated how many

Scholefield 2012 (*Continued*)

		people were lost to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Segnan 2002

Methods	See Segnan 2011. This report includes the baseline findings and complications to screening in the Italian trial. Patient satisfaction was assessed among screened persons by a questionnaire to be filled out immediately after the flexible sigmoidoscopy
Participants	See Segnan 2011
Interventions	See Segnan 2011
Outcomes	Complications to flexible sigmoidoscopy screening and follow-up colonoscopy Patient satisfaction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	See Segnan 2011
Allocation concealment (selection bias)	Low risk	See Segnan 2011
Blinding (performance bias and detection bias) All outcomes	Low risk	See Segnan 2011
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Segnan 2011
Selective reporting (reporting bias)	Low risk	See Segnan 2011
Other bias	Low risk	See Segnan 2011

Segnan 2011

Methods	Participants were recruited in a two-step procedure between June 1995 and May 1999. Eligible individuals first received an interest-in-screening questionnaire by mail designed to assess eligibility for and interest in screening. Responders who reported interest in screening, were randomised 1:1 into an intervention group or a control group. The control group was not contacted further. In three regions, randomisation was on an individual basis, and in the other three regions, a cluster randomisation model was adopted with the general practice as the cluster unit. Follow-up data was obtained from local hospital discharge records, pathology department files, population cancer registries and regional mortality registries. Death certificates were retrieved of all patients diagnosed with CRC during follow-up and supplemented with clinical information when available. Median follow-up for incidence was 10.5 years and for mortality 11.4 years
Participants	Individuals aged 55-64 in 6 regions in Italy. People were excluded if they reported a history of CRC, colorectal adenomas, inflammatory bowel disease, colorectal endoscopy in the previous two years, had two or more first degree relatives with CRC or had a medical condition that would preclude benefit from screening
Interventions	Flexible sigmoidoscopy once only and referral for colonoscopy if: Polyp > 5 mm, inadequate bowel preparation and at least one polyp, 3 or more adenomas, adenomas with villous component greater than 20% or high-grade dysplasia or CRC at the prevalent screening procedure. In addition, attenders were referred for colonoscopy if clinically indicated, judged by the physician who performed the screening procedure
Outcomes	CRC incidence, CRC mortality, all-cause mortality
Notes	Compliance with screening reported by the authors was 58.3% (of those who reported interest in screening). On the population-level, compliance will be lower due to the two-step invitation procedure. Cluster randomisation was not accounted for in the statistical analyses, and intra-cluster correlation was not computed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence
Allocation concealment (selection bias)	Low risk	Allocation concealment was secured by using a computer-generated allocation algorithm
Blinding (performance bias and detection bias) All outcomes	Low risk	The independent investigators who assessed outcomes were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	280 (1.6%) individuals in the intervention group and 324 (1.9%) in the control group could not be traced

Segnan 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	No other threats to validity detected

Taylor 2000

Methods	See Atkin 2010. Attenders in the first two screening centres received a questionnaire 3-6 months after the screening procedure to assess the participants' satisfaction with the screening. Individuals were grouped according to outcome of the flexible sigmoidoscopy screening as described in Miles 2003. In addition, a randomly selected sample of 60 participants, 10 men and 10 women from each of the three outcome groups, had a semi-structured interview
Participants	See Atkin 2010
Interventions	Mailed questionnaire 3 months after screening and semi-structured interview
Outcomes	Participants' satisfaction
Notes	The no-risk and low-risk group only had flexible sigmoidoscopy, while the high-risk group had both flexible sigmoidoscopy and full colonoscopy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Thiis-Evensen 1999

Methods	Participants were randomly drawn from the population registry of Telemark county, Norway, to the intervention group or control group. People in the intervention group were born in January or February. Controls were drawn irrespective of month of birth. Intervention with flexible sigmoidoscopy was performed in March and April 1983. Controls were not contacted at this point. Those who accepted invitation for screening in 1983 and all individuals in the control group were invited for colonoscopy in 1996. Two individuals were not invited due to emigration. Outcomes were obtained from public registries. Two, 12 and 73 weeks after the colonoscopy, the attendants received a questionnaire designed to evaluate the experience of taking part in the study. Follow-up was 13 years
Participants	Individuals aged 50-59 years living in Telemark county, Norway, in 1983. Individuals with a history of CRC were not excluded
Interventions	People in the intervention group were offered flexible sigmoidoscopy. All participants with any polyp at the baseline flexible sigmoidoscopy were referred for colonoscopy within two months. Those with polyps 5 mm or larger in diameter during the work-up colonoscopy had their polyps removed by polypectomy and were offered a repeat colonoscopy in 1989 and 1993. Those with polyps measuring less than 5 mm were not offered polypectomy in 1983, but had a colonoscopy and polypectomy in 1985 and were offered colonoscopy in 1989 and 1993
Outcomes	CRC incidence, CRC mortality, CRC from all causes, compliance with screening, patients' experience as participants in the trial, complications to the endoscopic examinations
Notes	All-cause mortality significantly higher in the intervention group than in the control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Participants in the intervention group drawn from eligible individuals born in January and February, while controls were drawn irrespectively of month of birth
Allocation concealment (selection bias)	Low risk	Randomisation based on social security number
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcomes were obtained from public registries
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two individuals could not be traced
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported

Thiis-Evensen 1999 (*Continued*)

Other bias	Low risk	No other threats to validity detected

Wardle 2003

Methods	See Atkin 2010. This study reports two studies. In study 1, individuals who had a flexible sigmoidoscopy screening procedure (participants) in two screening centres received a questionnaire assessing the impact on screening on selected psychological issues by mail 3 months after attendance. In study 2, a random selected sample of participants also received a questionnaire before the screening procedure, making it possible to trace changes in selected psychological issues. Individuals in both studies were grouped and compared according to outcome of the screening procedure as described in Miles 2003
Participants	See Atkin 2010
Interventions	Questionnaire before screening with flexible sigmoidoscopy (study 2) and 3 months after screening (study 1 and 2)
Outcomes	Psychological adverse effect of screening with flexible sigmoidoscopy
Notes	No no-screen control group. Short follow-up. The no-risk and low-risk group only had flexible sigmoidoscopy, while the high-risk group had both flexible sigmoidoscopy and full colonoscopy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable
Allocation concealment (selection bias)	Unclear risk	Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable
Selective reporting (reporting bias)	Unclear risk	Not applicable
Other bias	Unclear risk	Not applicable

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berry 1997	FOBT once only
Brevinge 1997	FOBT once only
Denis 2009	Non-randomised study
Faivre 2004	Non-randomised study
Li 2003	FOBT once only
Rasmussen 1999	FOBT once only
Selby 1988	Quasi-randomised trial
Thiis-Evensen 2001	CRC-mortality not reported
Winawer 1993	Non-randomised study
Zheng 2003	FOBT once only

Characteristics of ongoing studies *[ordered by study ID]*

Paimela 2010

Trial name or title	National cancer screening program in Finland
Methods	Age-eligible individuals living in municipalities which volunteered to implement screening were randomised 1:1 to the intervention group or control group. Individuals in the control group were offered the same intervention six years after start of screening in the intervention group (in 2010) in a staged fashion. Follow-up is passive through public registries
Participants	People aged 60-64 years living in participating municipalities in Finland. 52,998 subjects were randomised to the intervention group, and 53,002 subjects to the control group
Interventions	Biennial unrehydrated guaiac-based FOBT until age 69. Dietary and vitamin C restriction applied. 2 samples collected from 3 consecutive stools. Screen-positive referred for colonoscopy
Outcomes	CRC mortality
Starting date	September 2004
Contact information	Dr H.Paimela, e-mail: hannu.paimela@fimnet.fi

Paimela 2010 (*Continued*)

Notes	

DATA AND ANALYSES

Comparison 1. Screening procedures versus control - all studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Colorectal cancer mortality	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Flexible sigmoidoscopy	5	414754	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.65, 0.79]
1.2 Faecal occult blood testing - all studies	4	329642	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.82, 0.92]
1.3 Faecal occult blood testing - biennial screening only	4	305583	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.93]
2 Colorectal cancer incidence	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Flexible sigmoidoscopy	5	414754	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.74, 0.90]
2.2 Faecal occult blood testing - all studies	4	329516	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.02]
2.3 Faecal occult blood testing - biennial testing only	4	305515	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
3 All-cause Mortality	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Flexible sigmoidoscopy	4	359999	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
3.2 Faecal occult blood testing - all studies	4	329642	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.99, 1.01]

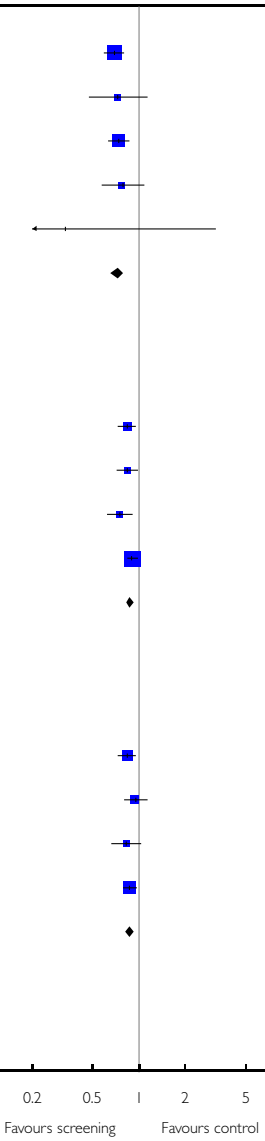
Analysis 1.1. Comparison 1 Screening procedures versus control - all studies, Outcome 1 Colorectal cancer mortality.

Review: Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals

Comparison: 1 Screening procedures versus control - all studies

Outcome: 1 Colorectal cancer mortality

Study or subgroup	Screening n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Flexible sigmoidoscopy					
Atkin 2010	221/57099	637/112939		47.3 %	0.69 [0.59, 0.80]
Hoff 2009	24/13653	99/41092		5.5 %	0.73 [0.47, 1.14]
Schoen 2012	252/77445	341/77455		37.7 %	0.74 [0.63, 0.87]
Segnan 2011 (1)	65/17136	83/17136		9.2 %	0.78 [0.57, 1.08]
Thiis-Evensen 1999	1/400	3/399		0.3 %	0.33 [0.03, 3.18]
Subtotal (95% CI)	**165733**	**249021**		**100.0 %**	**0.72 [0.65, 0.79]**
Total events: 563 (Screening), 1163 (Control)					
Heterogeneity: Chi^2 = 1.19, df = 4 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 6.39 (P < 0.00001)					
2 Faecal occult blood testing - all studies					
Kronborg 2004	362/30967	431/30966		19.0 %	0.84 [0.73, 0.96]
Lindholm 2008	252/34144	300/34164		13.2 %	0.84 [0.71, 0.99]
Mandel 1999	269/31157	177/15394		10.4 %	0.75 [0.62, 0.91]
Scholefield 2012	1176/76466	1300/76384		57.3 %	0.90 [0.84, 0.98]
Subtotal (95% CI)	**172734**	**156908**		**100.0 %**	**0.87 [0.82, 0.92]**
Total events: 2059 (Screening), 2208 (Control)					
Heterogeneity: Chi^2 = 3.64, df = 3 (P = 0.30); I^2 =18%					
Test for overall effect: Z = 4.67 (P < 0.00001)					
3 Faecal occult blood testing - biennial screening only					
Kronborg 2004	362/30967	431/30966		27.8 %	0.84 [0.73, 0.96]
Lindholm 2008	215/25655	300/34164		16.6 %	0.95 [0.80, 1.14]
Mandel 1999	148/15587	177/15394		11.5 %	0.83 [0.66, 1.03]
Scholefield 2012	593/76466	684/76384		44.1 %	0.87 [0.78, 0.97]
Subtotal (95% CI)	**148675**	**156908**		**100.0 %**	**0.87 [0.81, 0.93]**
Total events: 1318 (Screening), 1592 (Control)					
Heterogeneity: Chi^2 = 1.56, df = 3 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 3.79 (P = 0.00015)					



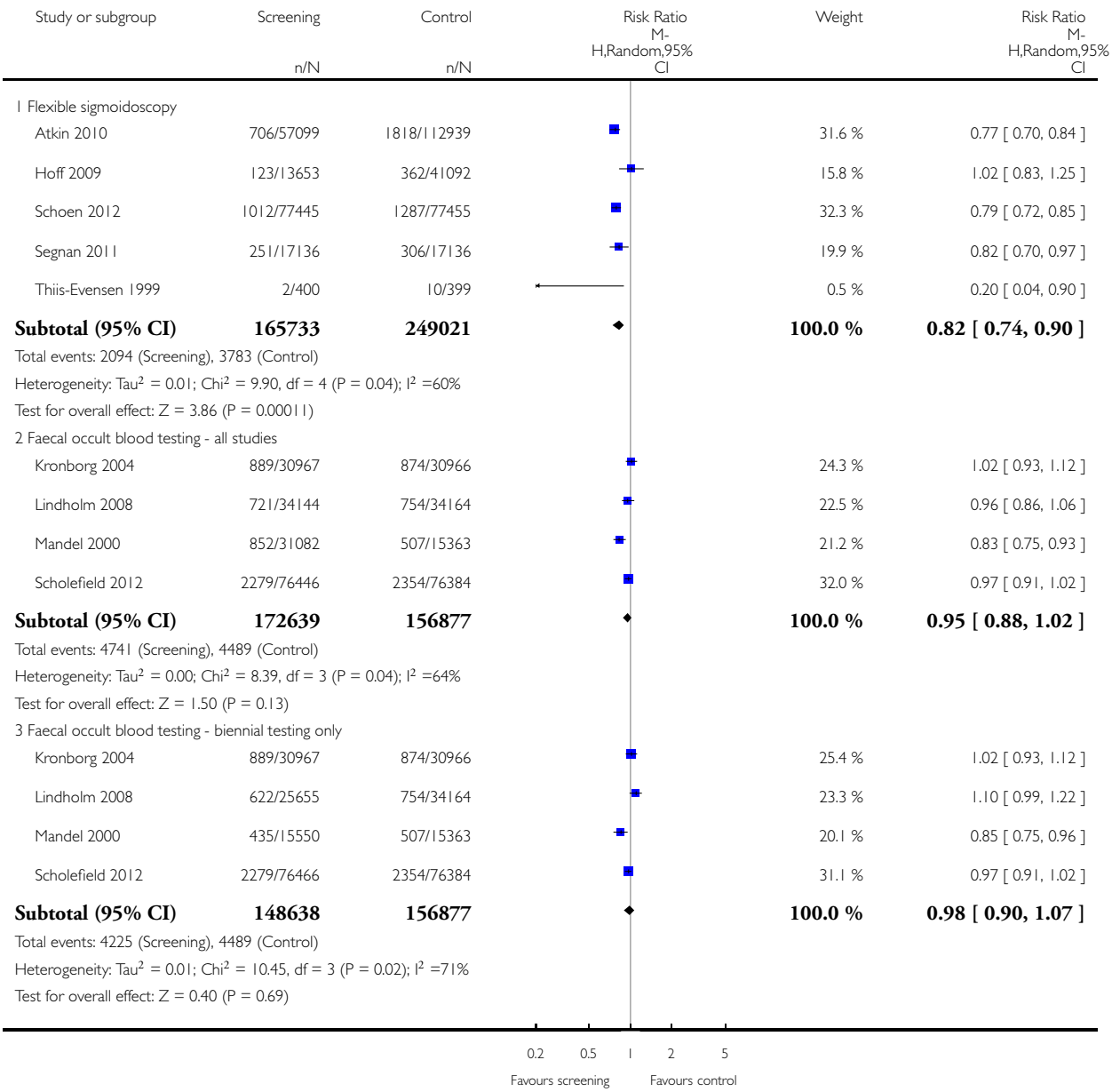
(1) Segnan 2011: Without adjustment for cluster randomisation.

Analysis 1.2. Comparison 1 Screening procedures versus control - all studies, Outcome 2 Colorectal cancer incidence.

Review: Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals

Comparison: 1 Screening procedures versus control - all studies

Outcome: 2 Colorectal cancer incidence

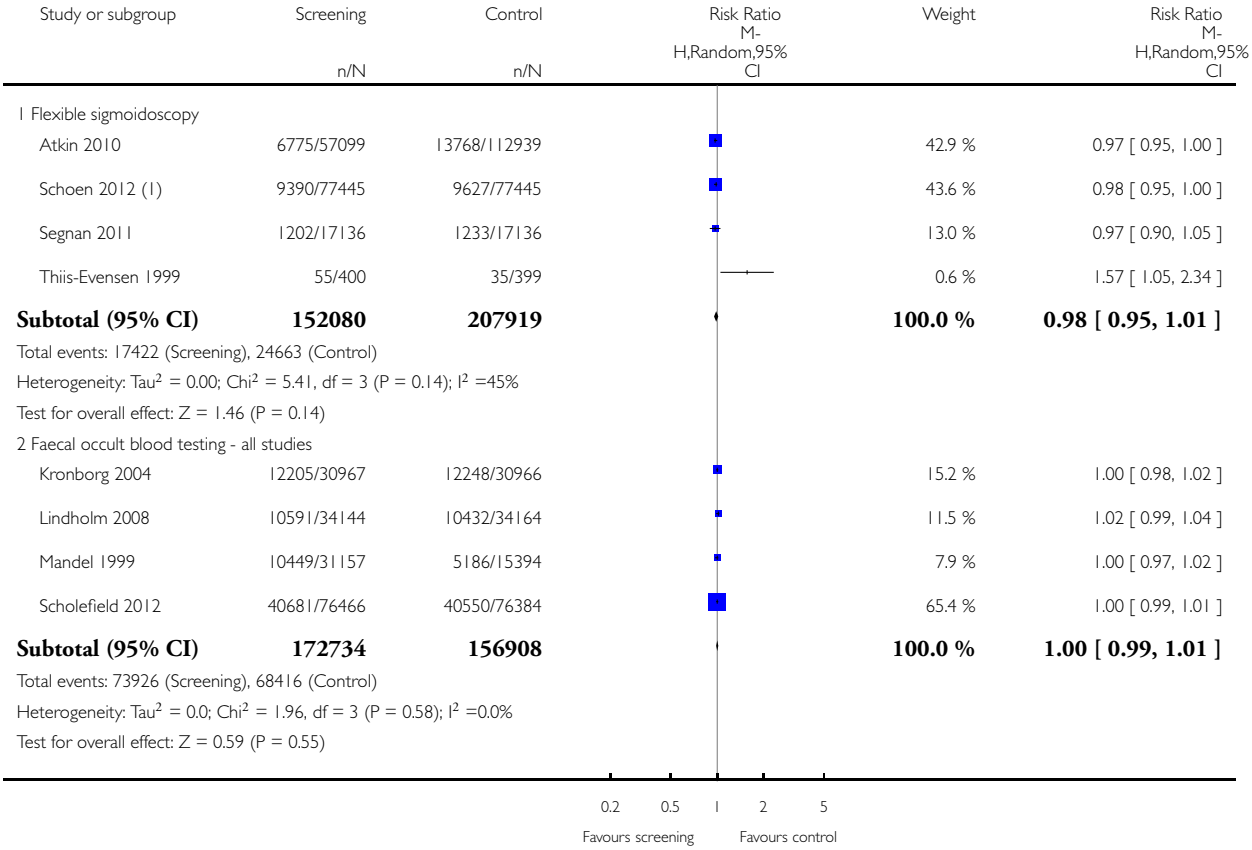


Analysis 1.3. Comparison 1 Screening procedures versus control - all studies, Outcome 3 All-cause Mortality.

Review: Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals

Comparison: 1 Screening procedures versus control - all studies

Outcome: 3 All-cause Mortality



(1) All cancer deaths due to colorectal, prostate, lung and ovarian cancer excluded.

ADDITIONAL TABLES

Table 1. Characteristics of included studies

Country	Design	Screening modality	Study period	Age	Control group (n)	Screening group (n)	Men/ Women (n)	Compliance+ (%)	Follow-up (years)
United States	Volunteers	gFOBT	1975-1992*	50-80	15394	A:15570 B:15587	22367/ 24184	A: 90 B: 90	18

Table 1. Characteristics of included studies (*Continued*)

England	Population based	gFOBT	1981-1995	45-74	76384	76466	72172/78079++	59	Median 11.7
Denmark	Population based	gFOBT	1985-2002	45-75	30966	30967	29714/32219	67	17
Sweden	Population based	gFOBT	1982-1995	60-64	34164	34144	NR	70	Median 15.5
United Kingdom	Volunteers	FS	1994-1999	55-64	112939	57099	83331/86707	71	Median 11.2
United States	Volunteers	FS	1993-2001	55-74	77455	77445	76684/78216	Single: 87 Dual: 51	Mortality: median 12.1 Incidence: median 11.9
Italy	Volunteers	FS	1995-1999	55-64	17136	17136	17234/17168	58	Mortality: median 11.4 Incidence: median 10.5
Norway (NORC-CAP)	Population based	FS	1999-2000	55-64	41092	13653	50%**	65	Mortality: Median 6 Incidence: median 7
Norway (TPS)	Population based	FS	1983	50-59	399	400	400/399	81	13

Characteristics of included studies. *Hiatus in screening 1982-1986, ** Actual figures not reported, A: Annual screening, B: Biennial screening, NR: Not reported, gFOBT: guaiac faecal occult blood test. FS: Flexible Sigmoidoscopy +At least 1 round in FOBT trials, ++Sum of men and women does not equal sum of screening and control group due to difference in reporting, please see characteristics of included studies for further explanation.

Table 2. Histologic classification of colorectal cancers in the screening and control groups

	Screening group Duke classification				Control group Duke classification			
Country	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
FOBT trials								
United States (annual screening)	107/354 (30%)	101/354 (29%)	80/354 (23%)	33/354 (9%)	88/394 (22%)	120/394 (30%)	82/394 (21 %)	65/394 (17%)
United States (biennial screening)	98/368 (27%)	95/368 (26%)	100/368 (27%)	41/368 (11%)	88/394 (22%)	120/394 (30%)	82/394 (21%)	65/394 (17%)
England	181/893 (20%)	286/893 (32%)	215/893 (24%)	192/893 (22%)	95/856 (11%)	285/856 (33%)	264/856 (31%)	179/856 (21%)
Denmark	105/481 (22%)	164/481 (34%)	90/481 (19%)	98/481 (20%)	54/483 (11%)	177/483 (37%)	111/483 (23%)	114/483 (24%)
Sweden	124/721 (17%)	261/721 (36%)	184/721 (26%)	152/721 (21%)	112/754 (15%)	260/721 (35%)	221/754 (29%)	161/754 (21%)
Flexible sigmoidoscopy trials								
United King-dom	NR							
United States	574/955 (60%)		381/955 (40%)		716/1253 (57%)		537/1253 (43%)	
Italy*	139/251 (55%)		112/251 (45%)		154/306 (50%)		152/306 (50%)	
Norway [+] (NORC-CAP)	33/123 (27%)		78/123 (63%)		62/362 (17%)		262/362 (72%)	
Norway (TPS)	1/2 (50%)	0/2	1/2 (50%)	0/2	0/10	5/10 (50%)	3/10 (30%)	2/10 (20%)

Stages of colorectal cancers diagnosed in the screening and control groups. *Cancers classified according to the Union for International Cancer Control as non-advanced (Stage I and II) or advanced (Stage III and IV). Non-advanced cancers equals Duke A and B. Advanced cancers equals Duke C and D. [+]The Norwegian NORCCAP trial classified cancers according to a modified Duke

classification system. Duke A and B cancers were classified as "localized", but Duke B cancers infiltrating neighbouring organs without distant metastasis were classified as "advanced". NR: Not reported.

Table 3. Physical complications to screening

Study	Flexible sigmoidoscopy	Colonoscopy	Bleeding[1]	Perforation	Death<30day of procedure[2]	Death <30 days of surgery	Major complications[3]	Miscellaneous
United States (gFOBT)		12246	11	4	NR	NR	NR	NR
United States (FS)	107236		NR	3	NR	NR	NR	NR
		17672	NR	19	NR	NR	NR	NR
England (gFOBT)		1474	1	5	0	5 [4]	0	1[5]
Sweden (gFOBT)	2108		0	3	0	0	0	14[15]
		190	1	2	0	0	0	
Norway (FS, NORC-CAP)[6]	12960		0	0	NR	0	0	38[7]
		2524	4	6	NR	0	0	41[7]
United Kingdom (FS)	40332[8]		12[9]	1	6 [10]	4 [11]	3[12]	13[13] 172[7]
		2377	9	4	1 [14]			7[7]
Italy (FS)	9911		0	1	NR	NR	NR	60[7]
		775	1	1	NR	NR	NR	30[7]
Norway (FS, TPS)	324		0	0	0	0	0	NR
		302	0	0	0	0	0	NR
TOTAL	**172871**		**12**	**5**	**6**	**4**	**3**	**376**
		37560	**27**	**22**	**1**	**5**		

[1] Those admitted to hospital due to bleeding
[2] Death within 30 days of endoscopic screening or work-up
[3] Bleeding, perforation and death excluded
[4] Myocardial infarction, 1 anastomotic leak, 2 pulmonary embolus, 1 carcinomatosis
[5] Snare entrapment
[6] Includes individuals aged 50-64 years

[7] Minor events not requiring hospitalisation
[8] 342 individuals had a baseline colonoscopy screening procedure due to strong family history of CRC and is included in the colonoscopy figures
[9] Includes 3 individuals with glutaraldehyde colitis
[10] 3 myocardial infarction, 1 cardiomyopathy, 1 intracerebral haemorrhage, 1 lung cancer
[11] 2 cardiovascular, 1 respiratory, 1 septicaemia
[12] 2 myocardial infarction, 1 pulmonary embolus
[13] 5 cases of definite glutaraldehyde colitis and 8 probable cases
[14] Myocardial infarction
[15] 14 patients who had a laparotomy had complications which prolonged their hospital stay
FS: Flexible sigmoidoscopy. gFOBT: Faecal occult blood test. NORCCAP: Norwegian colorectal cancer prevention trial. TPS: Telemark polyp study

Table 4. Mortality rates in screening and control groups

		Screening group			Control group			Risk ratio (95% CI)
Study	**Screening modality**	**Personyear**	**Deaths (n)**	**Deaths/ 100000py**	**Personyear**	**Deaths (n)**	**Deaths/ 100000py**	
US (annual)	gFOBT	240325	121	50	237420	177	75	0.68 (0.54-0.96)
US (biennial)	gFOBT	240163	148	61	237420	177	75	0.83 (0.66-1.03)
England	gFOBT	1296712	1176	91	1296614	1300	100	0.91 (0.84-0.98)
Denmark	gFOBT	431190	362	84	430755	431	100	0.84 (0.73-0.96)
Sweden	gFOBT	471072	252	53	471980	300	64	0.84 (0.71-0.99)
UK	FS	620045	189	30	1224523	538	44	0.69 (0.59-0.82)
US	FS	868966*	252	29	874358*	341	39	0.74 (0.63-0.88)
Italy	FS	186745	65	35	187532	83	44	0.78 (0.57-1.08)
Norway (NORC-CAP)	FS	NR	24	NR	NR	99	NR	0.73 (0.47-1.14)

Table 4. Mortality rates in screening and control groups (*Continued*)

Norway (TPS)	FS	NR	1	NR	NR	3	NR	0.33 (0.03-3.18)

Mortality rates in screening and control groups, NR: Not reported; gFOBT: guaiac faecal occult blood test; FS: Flexible sigmoidoscopy; py: person year; US: United States; UK: United Kingdom. *Estimated numbers.

Table 5. Incidence rates in screening and control groups

		Screening group			Control group			Risk ratio (95% CI)
Study	**Screening modality**	**Personyear**	**Cases (n)**	**Cases/ 100000py**	**Personyear**	**Cases (n)**	**Cases/ 100000py**	
US (annual)	gFOBT	235584	417	177	232612	507	218	0.81 (0.72-0.92)
US (biennial)	gFOBT	235513	435	184	232612	507	218	0.85 (0.75-0.96)
England	gFOBT	1286526	2279	177	1286877	2354	183	0.97 (0.91-1.03)
Denmark	gFOBT	431190	889	206	430755	874	203	1.02 (0.93-1.12)
Sweden	gFOBT	471072	721	153	471980	754	160	1.10 (0.99-1.22)
UK	FS	620045	706	114	1224523	1818	148	0.77 (0.70-0.84)
US	FS	850420*	1012	119	846710*	1287	152	0.78 (0.72-0.85)
Italy	FS	174177	251	144	173437	306	176	0.82 (0.70-0.97)
Norway (NORCCAP)	FS	91449*	123	135	274242*	362	132	1.02 (0.83-1.25)
Norway (TPS)	FS	NR	2	NR	NR	10	NR	0.20 (0.04-0.90)**

Incidence rates in screening and control groups. *Estimated numbers; **From publication; gFOBT: guaiac faecal occult blood test; FS: Flexible sigmoidoscopy; py:person year; CI: Confidence interval; US: United States; UK: United Kingdom; NR: Not reported.

APPENDICES

Appendix 1. MEDLINE (faecal occult blood) search strategy

#1 exp Colorectal Neoplasms/
#2 exp Colonic Neoplasms/
#3 exp Rectal Neoplasms/
#4 ((colorectal* or CRC or colon* or bowel* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or tumor* or tumour or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).mp.
#5 1 or 2 or 3 or 4
#6 exp Occult Blood/
#7 exp Immunochemistry/
#8 (faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa or heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe or hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure or hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or immocare or magstream or guaiac or occult blood or (stool adj3 occult) or (gaiac* adj2 smear*)).mp.
#9 ((((immunochemical* adj3 (test* or screen* or diagn*)) or immunologic*) adj3 (test* or screen* or diagn*)) or enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*).mp.
#10 6 or 7 or 8 or 9
#11 exp Mass Screening/
#12 exp Population Surveillance/
#13 (screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).mp.
#14 11 or 12 or 13
#15 5 and 10 and 14
#16 randomized controlled trial.pt.
#17 controlled clinical trial.pt.
#18 randomized.ab.
#19 placebo.ab.
#20 clinical trial.sh.
#21 randomly.ab.
#22 trial.ti.
#23 16 or 17 or 18 or 19 or 20 or 21 or 22
#24 humans.sh.
#25 23 and 24
#26 15 and 25

Appendix 2. MEDLINE (flexible sigmoidoscopy) search strategy

#1 exp Colorectal Neoplasms/
#2 exp Colonic Neoplasms/
#3 exp Rectal Neoplasms/
#4 ((colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).mp.
#5 1 or 2 or 3 or 4
#6 exp Endoscopy, Gastrointestinal/
#7 exp Colonoscopy/
#8 exp Sigmoidoscopy/
#9 exp Proctoscopy/
#10 (endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (flex* adj3 sig*)).mp.

#11 6 or 7 or 8 or 9 or 10
#12 exp Mass Screening/
#13 exp Population Surveillance/
#14 (screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
#15 12 or 13 or 14
#16 5 and 11 and 15
#17 randomized controlled trial.pt.
#18 controlled clinical trial.pt.
#19 randomized.ab.
#20 placebo.ab.
#21 clinical trial.sh.
#22 randomly.ab.
#23 trial.ti.
#24 17 or 18 or 19 or 20 or 21 or 22 or 23
#25 humans.sh.
#26 24 and 25
#27 16 and 26

Appendix 3. EMBASE (faecal occult blood) search strategy

#1 exp colorectal tumor/
#2 exp colorectal cancer/
#3 exp colorectal carcinoma/
#4 exp colorectal adenoma/
#5 exp colon tumor/
#6 exp colon cancer/
#7 exp colon carcinoma/
#8 exp colon adenoma/
#9 exp colon adenocarcinoma/
#10 exp rectum tumor/
#11 exp rectum cancer/
#12 exp rectum carcinoma/
#13 exp rectum adenoma/
#14 ((colorectal* or CRC or colon or colonic or bowel* or intestine or large intestine or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).m˙titl.
#15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
#16 exp occult blood/
#17 exp feces analysis/
#18 exp immunochemistry/
#19 (faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa or heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe or hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure or hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or immocare or magstream or guaiac or occult blood or (stool adj3 occult) or (gaiac* adj2 smear*)).mp.
#20 ((((immunochemical* adj3 (test* or screen* or diagn*)) or immunologic*) adj3 (test* or screen* or diagn*)) or enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*).mp.
#21 16 or 17 or 18 or 19 or 20
#22 exp mass screening/
#23 exp health survey/

#24 (screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).m˙titl.
#25 22 or 23 or 24
#26 15 and 21 and 25
#27 randomized controlled trial/
#28 randomization/
#29 controlled study/
#30 multicenter study/
#31 phase 3 clinical trial/
#32 phase 4 clinical trial/
#33 "human*".ti,ab.
#34 (animal* or nonhuman*).ti,ab.
#35 27 or 28 or 29 or 30 or 31 or 32
#36 33 and 34
#37 34 not 33
#38 35 not 37
#39 26 and 38
#40 (canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or bird* or fish* or trout*).m˙titl.
#41 39 not 40

Appendix 4. EMBASE (flexible sigmoidoscopy) search strategy

#1 exp colorectal cancer/
#2 exp colorectal tumor/
#3 exp colorectal carcinoma/
#4 exp colorectal adenoma/
#5 exp colon cancer/
#6 exp colon carcinoma/
#7 exp colon cancer/
#8 exp colon adenoma/
#9 exp colon adenocarcinoma/
#10 exp colon tumor/
#11 exp rectum cancer/
#12 exp rectum tumor/
#13 exp rectum carcinoma/
#14 exp rectum adenoma/
#15 ((colorectal* or CRC or colon or colonic or bowel* or intestine or large intestine or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).m˙titl.
#16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
#17 exp gastrointestinal endoscopy/
#18 exp colonoscopy/
#19 exp sigmoidoscopy/
#20 exp rectoscopy/
#21 (endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (flex* adj3 sig*)).mp.
#22 17 or 18 or 19 or 20 or 21
#23 exp mass screening/
#24 exp health survey/
#25 (screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).m˙titl.
#26 23 or 24 or 25
#27 16 and 22 and 26
#28 randomized controlled trial/

#29 randomization/
#30 controlled study/
#31 multicenter study/
#32 phase 3 clinical trial/
#33 phase 4 clinical trial/
#34 "human*".ti,ab.
#35 (animal* or nonhuman*).ti,ab.
#36 28 or 29 or 30 or 31 or 32 or 33
#37 34 and 35
#38 35 not 37
#39 36 not 38
#40 27 and 39
#41 (canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or #bird* or fish* or trout*).m˙titl.
#42 40 not 41

Appendix 5. The Cochrane Library (faecal occult blood) search strategy

#1 MeSH descriptor Colorectal Neoplasms explode all trees
#2 MeSH descriptor Colonic Neoplasms explode all trees
#3 MeSH descriptor Rectal Neoplasms explode all trees
#4 (colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Occult Blood explode all trees
#7 MeSH descriptor Immunochemistry explode all trees
#8 (faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa) or (heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe) or (hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure) or (hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or magstream or guaiac or occult blood) or (stool near3 occult) or (gaiac* near2 smear*)
#9 (immunochemical* near3 (test* or screen* or diagn*)) or (immunologic* near3 (test* or screen* or diagn*)) or (enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*)
#10 (#6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Mass Screening explode all trees
#12 MeSH descriptor Population Surveillance explode all trees
#13 (screen* or test*) or (population* near2 surveillance) or (early near3 detect*) or (early near3 prevent*)
#14 (#11 OR #12 OR #13)
#15 (#5 AND #10 AND #14)

Appendix 6. The Cochrane Library (flexible sigmoidoscopy) search strategy

#1 MeSH descriptor Colorectal Neoplasms explode all trees
#2 MeSH descriptor Colonic Neoplasms explode all trees
#3 MeSH descriptor Rectal Neoplasms explode all trees
#4 (colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Endoscopy explode all trees
#7 MeSH descriptor Colonoscopy explode all trees
#8 MeSH descriptor Sigmoidoscopy explode all trees

#9 MeSH descriptor Proctoscopy explode all trees
#10 (endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG) or (flex* near3 sig*)
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Mass Screening explode all trees
#13 MeSH descriptor Population Surveillance explode all trees
#14 (screen* or test*) or (population* near2 surveillance) or (early near3 detect*) or (early near3 prevent*)
#15 (#12 OR #13 OR #14)
#16 (#5 AND #11 AND #15)

FEEDBACK

Risk of bias in included studies, 25 October 2013

Summary

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Comment: In the present study's paragraph "Risk of bias in included studies" Holme et al. write: "In general, the risk of bias was judged as low." In the paragraph "Characteristics of included studies" the four randomised controlled trials (RCTs) on faecal occult blood test screening (FOBT-screening) are all judged by Holme et al. to have low risk of bias in six bias-categories except for the study by Kewenter et al. from 1994 where Holme et al. judge it to be unclear if there is any bias in the category "Random sequence generation (selection bias)".
In a previous study about potential biases in colorectal cancer screening using faecal occult blood test we identified six biases, of which five favour screening.(1) Therefore we concluded that a 16% relative risk reduction in colorectal cancer mortality found in the latest updated Cochrane review on FOBT-screening was overestimated. These identified biases in the four FOBT-screening RCTs could also affect the estimates calculated by Holme et al. in the present Cochrane review.
Reference List
(1) Riboe DG, Dogan TS, Brodersen J. Potential biases in colorectal cancer screening using faecal occult blood test. J Eval Clin Pract 2012 Feb 14.
I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Reply from authors received November 8th, 2013.
We thank Dr Brodersen for his comment to our review. In their cited article, Brodersen et al identified six potential biases which may have overestimated the effect of FOBT screening on colorectal cancer mortality and focused on the CRC screening specific items mode of detection, place of surgery and diagnostic delay. 1 We regret that Brodersen et al did not receive replies from other authors than those of the Funen trial in their effort to assess whether there actually were important biases in the four FOBT trials. All of the three biases mentioned arise when the participants included in the trial are treated differently than those who are selected as controls. In general it may be difficult to determine whether a difference in follow-up and treatment is a bias or a part of the intervention.
We agree with Brodersen et al that if controls had a less sensitive follow-up (e.g. distal endoscopy plus double contrast barium enema) than screenees (e.g. colonoscopy) and were treated in less specialized centers, the results could be biased in favor of screening. However, for example, in the Funen trial, only 22% of cancers were detected at screening (197 out of 889). 2 The other 78% of the cancers in the screening group were symptomatic CRCs which presumably had a work-up similar to the general population. Regarding treatment at specialized centers, 62.4% of screenees in the Funen trial were treated at the University hospital compared to 50% of controls. This

is a rather small difference, especially when taken into account that there were more early stage CRCs in the screening group compared to the control group.3 We do not agree with Brodersen et al that a difference in diagnostic delay is a bias. This is one of the benefits of screening. When an individual tests positive for occult blood in the stool, this prompts immediate evaluation of the colorectum. As clinical symptoms of colorectal cancer are often nonspecific, a longer diagnostic delay is anticipated and is not a bias. Whether the potential biases that Brodersen points out are clinically significant is difficult to quantify. In a study from France, people who had access to the same health care facilities (e.g. no differences in treatment or diagnostic follow-up between controls and screenees) were either invited to be screened with biennial FOBT or to receive care as usual and followed for 11 years. 4 In this trial, CRC mortality was reduced by 16% which is identical to the CRC mortality reduction reported on in the previous review of the four FOBT trials with similar length of follow-up. 5

Øyvind Holme
Michael Bretthauer
Geir Hoff
Atle Fretheim

1. Riboe DG, Dogan TS, Brodersen J. Potential biases in colorectal cancer screening using faecal occult blood test. J Eval Clin Pract 2013;19:311-6.
2. Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004;39:846-51.
3. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467-71.
4. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology 2004;126:1674-80.
5. 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:CD001216.

Contributors

see above

Comment to the reported total mortality, 22 November 2013

Summary

From Julian Treadwell
email address: jools.jt@zen.co.uk
Affiliation: NHS
Role: GP

The absence of any change in total mortality is explained as being due to under -powering of the review. Is this really the case with such large populations being observed? How are we to separate out deaths caused by extra interventions in the screened population- direct or indirect?

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Risk of bias in included studies, part 2, 17 December 2013

Summary

Comment: I would like to thank Holme et al. for their reply and I am happy that the authors of the present Cochrane review have recognised that we have identified six types of biases in the four RCTs on FOBT-screening.(1) Five of these six biases will for sure favour the screening effect and will therefore to a more or lesser extent overestimate the effect of FOBT-screening. The direction of the sixth bias (Change of FOBT during the study) in unknown. In relation to four of five screening-favouring biases there was absence of evidence of these biases in three of the four FOBT-trials because the primary investigators of these three RCTs were not willing to answer our questions about the potential biases.(1) This most raise great concern when appraising the validity of these studies.

Three of the six identified biases were performance bias, where there were differences in the care provided to each group.(1) Holme et al. recognise that two of three performance biases may result in an overestimation of the FOBT-screening effect. However, Holme et al. do not agree that a difference in diagnostic delay is a bias. Holme et al. writes: "This is one of the benefits of screening. When an individual tests positive for occult blood in the stool, this prompts immediate evaluation of the colorectum. As clinical symptoms of colorectal cancer are often nonspecific, a longer diagnostic delay is anticipated and is not a bias." However, it is not this kind of delay we are revealing and discussing in our paper.(1) The kind of delay Holme et al. is describing is either what is called patient delay or doctor's delay - or both? The delay we are discussing is system delay. What we are emphasising is that also the control group has to be offered effective care: effective diagnostic procedures and treatment. It is always relevant to ask in a screening-RCT whether both screened and unscreened populations had equal chances of receiving effective care. If a cancer screening-RCT is conducted in a country where the healthcare system is inadequately organised screening will most likely have a positive effect on the specific cancer mortality: if patients in the control group (that have symptoms from the cancer screened for) receive unnecessary long waiting time before they are offered adequate examinations and later treatment, then screening will always have a positive effect on the specific cancer mortality if the patients in the screened group are in contrast offered an effective diagnostic pathway and treatment. This positive effect on the specific cancer mortality is an effect of an adequate effective care versus an inadequate and ineffective care plus may be a screening effect.

In conclusion, there is a high risk of bias in the four RCTs on FOBT-screening. I think that Holme et al. should recognise these facts and as a minimum take the biases in account when they update their Cochrane review.

Reference List

(1) Riboe DG, Dogan TS, Brodersen J. Potential biases in colorectal cancer screening using faecal occult blood test. J Eval Clin Pract 2012 Feb 14.

Reply

We thank Dr Brodersen for his valuable comments. We agree that the introduction of screening has effects on patient management and care and that this effect in itself is an important contributor to improved mortality for the disease screened for (irrespective of the effect of the screening intervention itself). This has been clearly demonstrated in mammography screening 1and is presumably also apparent in CRC screening. We will take his considerations into account when updating the review.

With respect to differences in system delay in Denmark, we emphasized in our previous reply that the difference may be largely explained by the different indication for examination (positive FOBT versus symptoms, which in colorectal cancer often is nonspecific). In the Funen trial, time from positive FOBT to colonoscopy was 24 days. 2In the published data from Denmark3, the total system delay was 56 days, including delay from diagnosis to treatment, and is thus not completely comparable to the results from the Funen trial.

Øyvind Holme

Michael Bretthauer

Atle Fretheim

Reference list:

1. Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. N Engl J Med 2010;363:1203-10.

2. Riboe DG, Dogan TS, Brodersen J. Potential biases in colorectal cancer screening using faecal occult blood test. J Eval Clin Pract 2013;19:311-6.

3. Hanssen R, 2008. (Accessed Jan 9th, 2014, at http://folkesundhed.au.dk/fileadmin/www.folkesundhed.au.dk/forskningsenheden˙for˙almen˙praksis/publikationer/udgivelser/afhandlinger/cd.pdf.)

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 25 March 2013.

Date	Event	Description
6 March 2014	Feedback has been incorporated	New feedback from John Brodersen and authors reply incorporated

HISTORY

Protocol first published: Issue 8, 2011

Review first published: Issue 9, 2013

Date	Event	Description
6 December 2013	Feedback has been incorporated	Two feedback incorporated with Authors reply to the one by Brodersen

CONTRIBUTIONS OF AUTHORS

AF and MB had the original idea for the review. OH was responsible for drafting the protocol and the first draft of the review. OH and MB performed data extraction and assessed risk of bias of included studies. JOJ was responsible for statistical analyses. All authors participated in writing the manuscript, interpretation of results and approval of the final version of the review.

DECLARATIONS OF INTEREST

GH is the principal investigator of the NORCCAP and TPS trials. MB and OH are co-investigators of the NORCCAP trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

*Occult Blood; *Sigmoidoscopy [adverse effects; mortality]; Colonic Neoplasms [*diagnosis; mortality]; Colonoscopy [adverse effects; mortality]; Guaiac; Indicators and Reagents; Randomized Controlled Trials as Topic; Rectal Neoplasms [*diagnosis; mortality]

MeSH check words

Humans