Screening for colorectal cancer using the faecal occult blood test, Hemoccult (Review)

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[Intervention Review]

Screening for colorectal cancer using the faecal occult blood test, Hemoccult

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ABSTRACT

Background

Colorectal cancer is a leading cause of morbidity and mortality, especially in the Western world. The human and financial costs have prompted considerable research to evaluate screening tests to detect the cancer at an early curable stage. Tests that have been considered for population screening include the faecal occult blood test (FOBT), flexible sigmoidoscopy and colonoscopy. Reducing mortality from colorectal cancer (CRC) may be achieved by the introduction of population-based screening programmes.

Objectives

To determine whether screening for colorectal cancer using the faecal occult blood test (guaiac or immunochemical) reduces colorectal cancer mortality and to consider the benefits and harms of screening.

Search methods

Published and unpublished data for this review were identified by:

Reviewing studies included in the previous Cochrane review;

Searching several electronic databases (Cochrane Library, Medline, Embase, CINAHL, PsychInfo, Amed, SIGLE, HMIC); and

Writing to the principal investigators of potentially eligible trials.

Selection criteria

We included all randomised trials of screening for colorectal cancer that compared faecal occult blood test (guaiac or immunochemical) on more than one occasion with no screening and reported colorectal cancer mortality.

Data collection and analysis

Data from the eligible trials were independently extracted by two reviewers. The primary data analysis was performed using the group participants were originally randomised to ('intention to screen'), whether or not they attended screening; a secondary analysis adjusted for non-attendance. We calculated the relative risks and risk differences for each trial, and then overall, using fixed and random effects models (including testing for heterogeneity of effects). We identified nine articles concerning four randomised controlled trials and two controlled trials involving over 320,000 participants with follow-up ranging from 8 to 18 years.

Main results

Combined results from the 4 eligible randomised controlled trials shows that participants allocated to FOBT screening had a statistically significant 16% reduction in the relative risk of colorectal cancer mortality (RR 0.84; CI: 0.78-0.90). In the 3 studies that used biennial screening (Funen, Minnesota, Nottingham) there was a 15% relative risk reduction (RR 0.85, CI: 0.78-0.92) in colorectal cancer mortality. When adjusted for mean screening attendance in the individual studies, there was a 25% relative risk reduction (RR 0.75, CI: 0.66 - 0.84) for those attending at least one round of screening using the faecal occult blood test.

Authors' conclusions

Benefits of screening include a modest reduction in colorectal cancer mortality, a possible reduction in cancer incidence through the detection and removal of colorectal adenomas, and potentially, the less invasive surgery that earlier treatment of colorectal cancers may involve.

Harmful effects of screening include the psycho-social consequences of receiving a false-positive result, the potentially significant complications of colonoscopy or a false-negative result, the possibility of overdiagnosis (leading to unnecessary investigations or treatment) and the complications associated with treatment.

PLAIN LANGUAGE SUMMARY

Screening for colorectal cancer using the faecal occult blood test, Hemoccult

Regular screening of faeces for blood can detect colorectal cancer earlier and hence may reduce mortality in populations at risk, such as older patients. The screening test used in these trials to detect colorectal (bowel) cancer was the faecal occult blood test (FOBT). If the FOBT is positive, the bowels are examined closely with further diagnostic test (coloscopy, flexible sigmoidoscopy, double-contrast barium enema), but these tests often cause discomfort and can cause serious adverse consequences. As blood identified in faeces may be due to several reason (unrelated to cancer), it may cause people unnecessary stress and expose them to possible harm. This review found that FOBT screening is likely to avoid approximately 1 in 6 colorectal cancer deaths.

BACKGROUND

Colorectal cancer is a leading cause of morbidity and mortality, especially in the Western world. Colorectal cancer is the third most commonly diagnosed cancer in males (54.8 per 100,000) and the second in females (34.8 per 100,000) in the United Kingdom (ONS 2005). In the USA, it is the third most commonly diagnosed cancer in both males (62.7 per 100,000) and females (45.8 per 100,000) (U.S. CDC 2004). Colorectal cancer is the second most commonly diagnosed cancer for males (60.7 per 100,000) and for females (52.1 per 100,000) in Australia (AIHW 2001).

The human and financial costs of this disease have prompted considerable research efforts to evaluate the ability of screening tests to detect the cancer at an early curable stage. Tests that have been considered for population screening include variants of the faecal occult blood test, flexible sigmoidoscopy and colonoscopy (Winawer 1993). Reducing mortality from colorectal cancer (CRC) may be achieved by the introduction of population-based screening programmes.

OBJECTIVES

The primary objective of the review were to determine whether screening for colorectal cancer using the faecal occult blood test (guaiac or immunochemical) reduces colorectal cancer mortality and, secondarily, to evaluate the range of benefits and harms of screening.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of screening for colorectal cancer using repeated faecal occult blood test (guaiac or immunochemical) were considered for inclusion in the review.
For the primary analysis we included trials that used randomisation of individuals or groups.

Types of participants

Adults (18 years or over) participating in controlled colorectal cancer screening trials, either ongoing or completed. Trial participants may be 'volunteers' who agreed to take part in the trial, or individuals or households identified from general practitioner records or population registers.

Types of interventions

Screening using the faecal occult blood test (guaiac or immunochemical) that were undertaken by participants on more than one occasion (e.g. either annually or biennially). The guaiac test slides may or may not be rehydrated.
Investigation following a positive faecal occult blood test may be colonoscopy or sigmoidoscopy and double contrast barium enema, with removal of colorectal neoplasms (cancers or adenomas) found at diagnostic investigation.

Types of outcome measures

The primary outcome was reported colorectal cancer mortality in the screening and control groups.
Other process measures assessed included:

- the sensitivity of the faecal occult blood test (guaiac or immunochemical) for colorectal cancer,
- the proportion of those allocated to screening who actually attended screening,
- colorectal cancer incidence in the screening and control groups,
- colorectal cancer staging in the screening and control groups,
- all cause mortality in the screening and control groups

We also looked at the physical harms of follow-up colonoscopy or sigmoidoscopy (e.g. reported bowel perforations and haemorrhages due to these procedures).
Other important outcomes not explored in this review at this stage included:

- the disruption screening causes to people's lives,
- the stress and discomfort from testing and follow-up investigations,
- the anxiety caused by falsely positive screening results,
- potential advantages of surgery performed earlier (i.e., for early colorectal cancers).

Search methods for identification of studies

See: Colorectal Cancer search strategy.
This review is the second update of the previously published Cochrane Collaboration systematic review (First published 1998 Issue 2).
To identify appropriate studies, we conducted a search using COCHRANE LIBRARY, MEDLINE, EMBASE, CINAHL, PSYCHINFO, AMED, SIGLE, and HMIC electronic databases (searches performed using WebSPIRS - search strategies used available on request). There were no restrictions on language of the articles. Studies identified in the searches published before 1996 were compared with the existing reference list for the previous Cochrane review.
Four elements of the search strategy were developed and intersected using the Boolean term 'AND':
i. Colorectal cancer subject headings (exploded): colorectal neoplasms. Text words (title and abstract): colorectal*, colon, colonic, bowel*, rectal, rectum, sigmoid, anal, anus combined with cancer*, neoplas*, tumor*, tumour*, carcinoma*, sarcoma*, adenocarcinoma*, adeno?carcinoma*, adenom*, lesion*, CRC
ii. Diagnostic methods subject headings (exploded): occult-blood, endoscopy-gastrointestinal, colonoscopes, sigmoidoscope, proctoscope and enema. Text words (title and abstract): faecal, fecal, stool near occult, FOBT, FOB, haemoccult, hemoccult, sensa, coloscreen, seracult, ez-detect, colocare, flexsure, hemmoquant, hemeselect, immudia, monohaem, insure, !nsure, hemodia, instant-view, immocare, magstream, guaiac near1 smear*, endoscop*, proctoscop*; colonoscop*, sigmoidoscop*, rectosigmoidoscop*, proctosigmoidoscop*, COL, SIG, FSIG, barium near1 enema, DCBE
iii. Screening subject headings: mass screening, population surveillance. Text words (title and abstract): screen*, test, tests, testing, tested or population* near 1 surveillance, early near 3 detect*, early near 3 prevent*
iv. Study search criteria: based on the Cochrane controlled trial filter (Alderson 2005).

The references of all retrieved relevant studies were searched for additional trials. We also wrote to the principal investigators of four of the trials (Funen, Goteborg, Minnesota, Nottingham) to inform them of the update to the review. The trial authors were asked to clarify aspects of the methods and results, and asked for any unpublished data in the areas of quality and trial outcomes. Three of the four investigators replied (authors of the Nottingham trial did not respond).

2010 Update Search

For this update, searches was conducted in May 2010 to identify articles published between Januar 2006 to May 2010, in addition to the previously performed searches from 1989-2006. We searched COCHRANE LIBRARY, MEDLINE, EMBASE, CINAHL, and PSYCHINFO electronic databases (searches performed using OVID - search strategies used available on request). There were no restrictions on language of the articles. The update search strategy used the new Cochrane highly sensitive search filter (Cochrane Handbook 5.0.2), replacing the 'study search criteria' filter (Alderson 2005) above.

Data collection and analysis

Two reviewers (PH and PG) contributed to assembling a comprehensive set of articles published between 1989 and 2010 that met the inclusion criteria. The reference list was examined to make certain that the current searches did not miss studies included in the previous Cochrane review.

Data from the trials were independently extracted onto standardised critical appraisal forms by two reviewers (PH and EW). Abstracted data included the study citation, study objectives, study design, method of randomisation and blinded assessment of mortality, length of study and follow-up, number of participants (including number of withdrawals), participant characteristics, description of FOB testing regime, characteristics of FOB test (i.e., sensitivity, specificity and positive predictive value), compliance with screening (both overall and for each screening round), number of CRC cases, number of CRC deaths, all cause mortality, number of follow-up diagnostic procedures (e.g. colonoscopies, sigmoidoscopies, etc), compliance with follow-up diagnostic procedures and stage of cancer.

The trials identified from the searches were independently assessed for their quality by two reviewers (PH and EW), using the criteria recommended by the Cochrane Collaboration (Alderson 2005). Using the Cochrane approach to the assessment of allocation concealment, trials were graded as one of four randomisation categories (A = adequate; B = unclear; C = inadequate; D = not used). A method to generate the sequence of randomisation was regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next (e.g. table of random numbers or computer generated). Disagreements about quality were resolved through discussion with PG.

Data analysis was performed using the group subjects were originally randomised to ('intention to screen'), whether or not they were ever screened. To determine the effect of screening on colorectal cancer mortality, we estimated the relative risk and risk difference for each trial, and then overall, using fixed and random effects models and tested for heterogeneity of effects using the chi-squared test in Review Manager 5.0.2.

Since analysis by intention-to-screen would underestimate any real effect in those attending screening, as a secondary analysis, we adjusted for screening in individual trials using a previously published method (Glasziou 1992). Essentially, this method divides the intention-to-screen effect (relative risk reduction) by the proportion attending screening.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The original search (conducted in February 2005) retrieved a total of 4,565 citations. Of these, 1,087 abstracts were duplicates and were excluded, leaving 3,478 abstracts for further consideration. 112 abstracts were reviewed in detail with 21 articles retrieved to determine relevancy for inclusion in the review. Nine publications relating to four randomised controlled trials, and supplementary information from two non-randomised controlled trials, were considered in the updated review (please see table of included studies). An update search of the literature (conducted in February 2006) found a further 317 citations, but no articles were found relevant for inclusion in the review.

Results of the 2010 Update Search

The systematic searches identified 1,271 potentially relevant articles. After adjusting for duplicates, 859 articles remained. Of these, 852 studies were discarded as these papers clearly did not meet the inclusion criteria for the review. Of the 7 remaining studies reviewed in detail, 6 were excluded due to not including a control group.

16 studies were excluded from the review (see table of excluded studies) as ineligible. The cluster randomised trial performed in China (Jiashan: Jiashan 2003; Liu 2000) was excluded from the review as participants were screened only once using a reversed passive hemagglutination (RPHA) FOB test. The other nine studies (Almpoea 2004; California 1993; Calvados 1996; Florence 1997; Guildford 2001; Japan 1995; Milan 1999; New York 1993; Washington 1995) were excluded due to either being non-randomised or non-controlled trials, or used a FOB test on only one occasion in the screening group. Six studies identified in the 2010 update search (Italy 2010; Netherlands 2008; Netherlands 2009; Netherlands 2010; Turin 2010; Tuscany 2008) were excluded from

the review due to either being non-randomised or non-controlled trials group.

The four randomised controlled trials included in this review were reported in 12 published articles (Funen: Funen 1996, Funen 2002, Funen 2004; Goteborg: Goteborg 1994; Goteborg 1996, Goteborg 2008; Minnesota: Minnesota 1993, Minnesota 1999, Minnesota 2000; Nottingham: Nottingham 1996, Nottingham 1999, Nottingham 2002). One article (Goteborg 2008) was identified from the 2010 update search. The four randomised controlled trials involved 327,043 participants in Denmark, Sweden, USA and the UK.

Three trials - the Funen, Goteborg and Nottingham trials - randomly allocated individuals or households identified from general practice records or population registers to invitation with screening with Hemoccult (Nottingham) or Hemoccult-II (Funen, Goteborg) or to control groups. One trial - the Minnesota study - allocated people to either screening (Hemoccult) or control groups only after they had agreed to participate in the trial ('volunteers'). The age of participants ranged from 45 to 75 years for the majority of trials, with the exception of the Goteborg trial where participants were aged 60 to 64 years. The ratio of males and females was similar across the studies (see Table 1). The Funen trial (Funen 2004) reported that mean age increased from 59.8 years to 73.0 years during the study and that the male/female ratio decreased from 0.92 to 0.78. The length of follow-up ranged from 8.5 years to 18.4 years. Median follow-up for the Nottingham trial was 11.7 years (range 8.4 to 18.4 years) (Nottingham 2002) and mean follow-up time for the Goteborgtrial was 15.75 years (range 11.25 to 19.5 years) (Goteborg 2008).

Table 1: Age, percentage male/female, screening interval and length of follow-up for included trials.

RCTs	*Age*	*Male*	*Female*	*Screening*	*Follow-Up*
Nottingham	45-74	48%	52%	Biennial	11.7 yrs
Funen	45-75	49.6%	50.4%	Biennial	17 yrs
Goteborg	60-64	NR	NR	Biennial	15.75 yrs
Minnesota	50-80	48%	52%	Ann+Bien	18 yrs

Three trials (Funen, Goteborg, Nottingham) performed biennial screening. Only individuals who took part in the first round of screening were invited for further screening for the Funen trial. One randomised trial (Minnesota) evaluated both annual and biennial screening. The number of potential screening rounds varied between the trials. Nine rounds of screening were offered to the screening arm of the Funen trial. Participants in the screening arm of the Goteborg trial were offered a second FOB test one-and-a-half to two years after initial screening. In the Minnesota trial, the screening rounds were divided into Phase 1 (between February 1976 and December 1982) and Phase II (between February 1986 and February 1992). This meant that screening group participants had an interval of between 3 to 5 years between the two phases of the trial. In total, 11 rounds of screening were offered to the annual screening group and 6 rounds of screening were offered to the biennial screening group. Six rounds of screening were offered to participants in the screening arm of the Nottingham trial.

To reduce the rate of a false-positive results, three trials (Funen, Goteborg, Minnesota) encouraged participants to restrict their diet and medications for a specific period before collecting samples for the Hemoccult test. The restrictions varied between studies, but primarily concerned avoiding food containing blood (e.g. red meat, fish, poultry), certain fruits and vegetables, vitamin C and aspirin. Hemoccult slides were not rehydrated in two of the randomised trials (Funen, Nottingham) and both of the controlled trials. Both the Goteborg and Minnesota randomised trials rehydrated the majority of Hemoccult slides. In all of the trials, participants with a positive Hemoccult test were referred for further diagnostic evaluation. Further diagnostic evaluations were expected to be performed by colonoscopy, except for participants in the Goteborg randomised trial who received sigmoidoscopy and double-contrast barium enema.

Risk of bias in included studies

All of the randomised trials (Funen, Goteborg, Minnesota, Nottingham) used an adequate randomisation procedure resulting in comparable study groups. Given that the FOB test was completed by trial participants at home, blinding of participants to the intervention was not possible.

Mortality analyses were by "intention to treat" for the Funen, Minnesota and Nottingham randomised trials. This is not specifically stated for the Goteborg trial. One hundred and ninety-seven par-

ticipants were excluded from the screening group in the Goteborg randomised trials (participants had either died between randomisation and screening or could not be located).
Blinded, standardised assessment for mortality was performed for all four randomised controlled trials and both controlled trials. The Funen randomised trials included deaths from the complications of treatment for colorectal cancer in the colorectal cancer mortality analyses. This is not specifically stated for the other trials.

Effects of interventions

Meta-analysis of colorectal cancer screening results
Combining the four randomised trials shows that screening results in a statistically significant relative reduction in colorectal cancer mortality of 16% (fixed and random effects models: RR 0.84, CI: 0.78-0.90). This overall result combined the annual and biennial groups in the Minnesota randomised trial as there was little heterogeneity between the effects (Chi-square test for heterogeneity = 1.85, df = 3, P = 0.60, I^2 = 0%).
Sensitivity analysis
Combining the trials that used biennial screening (Minnesota, Nottingham, Goteborg) shows a 15% (fixed and random effects model RR 0.85, CI: 0.78-0.92) relative reduction in colorectal cancer mortality and a slightly larger confidence interval (Chi-square test for heterogeneity = 0.21, df = 3, P = 0.90, I^2 = 0%).

Reduction in mortality adjusted for attendance
The non-compliance rate for the trials ranged from 33% to 46% for the first screen and between 22% and 40% for at least one round of screening. When the relative risk is adjusted for attendance (see below) to screening in the randomised trials, the overall predicted relative mortality reduction is 25% (RR 0.75, CI: 0.66 - 0.84) for those screened (analysis not shown - available on request).
Individual trial results
Deaths attributed to colorectal cancer have been published for all of the four trials. The relative risk reductions for colorectal cancer mortality vary from 13% to 33% (see Table 2). The Minnesota randomised trial reported a 33% reduction (RR 0.67, 95% CI: 0.51-0.83) in colorectal cancer mortality for the annual screening group and a 21% reduction (RR 0.79, CI: 0.62-0.97) in colorectal cancer mortality for the biennial screening group at 18 years of follow-up (Minnesota 1999). The Goteborg randomised trial reported a 16% reduction (RR 0.84, 95%CI: 0.71-0.99) in colorectal cancer mortality (Goteborg 2008) for biennial screening after a mean 15 years and 9 months of follow-up. The Nottingham trial reported a 13% reduction (RR 0.87, CI: 0.78-0.97) in colorectal cancer mortality for biennial screening after 11 years of follow-up (Nottingham 2002). The Funen randomised trial reported a 16% reduction (RR 0.84, CI: 0.73-0.96) in colorectal cancer mortality for annual screening and an 11% reduction (RR 0.89, CI: 0.78-1.01) in colorectal cancer mortality, including deaths attributed to complications from treatment, for biennial screening at 17 years of follow-up (Funen 2004).
Table 2: Number of CRC deaths in screening and control groups, mortality incidence ratio and mortality reduction for included trials.

	No. of CRC deaths		Incidence Ratio		
RCTs	***Screen***	***Control***	***Screen***	***Control***	***Mort.Red.***
Nottingham	593/76466	684/76384	0.70/1000py	0.81/1000py	13%
Funen	362/30967	431/30966	0.84/1000py	1.00/1000py	16%
Goteborg	252/34144	300/34164	0.53/1000py	0.64/1000py	16%
Minnesota-A	121/15570	177/15384	0.67/1000	1.00/1000	33%
Minnesota-B	148/15587	-	0.79/1000	-	21%

All-cause mortality
All-cause mortality results are shown in Table 3. Combining the four trials did not show any significant difference in all-cause mortality between the screening and control groups (fixed effects model: RR 1.00, CI: 0.99-1.02; random effects model: RR 1.00, CI: 0.99-101). There was no important heterogeneity between trials (Chi-squared test for heterogeneity = 1.96, df = 3, p = 0.59, I^2 = 0%).
Furthermore, when excluding deaths from colorectal cancer, shows no significant change in non-colorectal cancer mortality between the screening and control groups (fixed and random effects model:

RR 1.01, CI: 1.00-1.03). There was no important heterogeneity between trials (Chi-squared test for heterogeneity = 1.42, df = 3, p = 0.70, I^2 = 0%).

Table 3: All-cause mortality and incidence ratios for included trials.

	Number of Deaths		Incidence Ratio for All-Cause Mortality	
RCTs	***Screen***	***Control***	***Screen***	***Control***
Nottingham	20421	20336	24.18/1000py	24.11/1000py
Funen	12205	12248	28.3/1000	28.4/1000
Goteborg	10591	10432	22.48/1000py	22.10/1000py
Minnesota	10449	5213	342-340/1000	343/1000

Attendance

The percentage of participants in the screening groups who completed at least one round of screening ranged from 60% to 78% (see Table 4). Compliance with screening was higher for the Minnesota trial than for the European trials. Hemoccult screening continued to be offered to all screening participants in most trials, regardless of previous attendance. In the Funen study, only subjects who participated in the first round of screening were invited to subsequent screening rounds, hence, the compliance with Hemoccult testing was very high (91-94%) (Funen 2004). This may affect the generalisability of the findings of the Funen study.

Table 4: Attendance at first screening round, subsequent screening rounds and at least one round for included trials.

RCTs	***First Screen***	***At least one***	***Subsequent rounds***
Nottingham	53.4%	59.6%	-
Funen	66.8%	-	91-94%(2-9)
Goteborg	63%	70%	60%
Minnesota	NR	75%-Ann; 78%-Bi	-

Test Accuracy

For two of the trials (Funen, Nottingham), the Haemoccult slides were not rehydrated resulting in a low test positivity rate (0.8% to 3.8%) and a higher positive predictive value for colorectal cancer (5% to 18.7%). In comparison, the test positivity rate for rehydrated slides (Goteborg and Minnesota) was 1.7% to 15.4% and the positive predictive value lower at 0.9% to 6.1% (see Table 5). The sensitivity of the Hemoccult test was defined as the proportion

of all colorectal cancers that were detected by screening, where "all colorectal cancers" was the sum of screen-detected cancers (true positives) and interval cancers within one or two years of screening (false-negatives). The estimated sensitivity of the Hemoccult test for colorectal cancer varied from 55% to 57% for the non-rehydrated slides (81% for a small sample of participants in the Minnesota trial) and from 82% to 92% for the rehydrated slides.

Table 5: Rehydration of slides, positivity rate, sensitivity, PPV for CRC and adenomas.

RCTS	*Rehyd.*	*Positivity Rate*	*Sensitivity*	*PPV (CRC)*	*PPV (Aden)*
Nottingham	No	1.2-2.7%	57.2%	9.9-17.1%	42.8-54.5%
Funen	No	0.8-3.8%	55%	5.2-18.7%	14.6-38.3%
Goteborg	Yes	1.7-14.3%	82%	4.8%	14.0%
	No	1.9%	NR	NR	NR
Minnesota	Yes	3.9-15.4%	92.2%	0.9-6.1%	6.0-11.0%
	No	1.4-5.3%	80.8%	5.6%	NR

Incidence and Stage

As population screening results in earlier cancer diagnosis, we would expect an excess of colorectal cancers detected initially in the screening groups. In the previous Cochrane review, the authors reported that there was an excess of CRC cases for the Funen, Goteborg and Nottingham trials. However, it was uncertain why this did not initially occur for the Minnesota trial (Towler 1998). A re-examination of this data shows an increased number of CRC cases for the screening groups in the Funen (at 3 years follow-up CRC cases screen = 147; CRC cases control = 115; Kronborg 1989), Goteborg (at 8.5 years follow-up CRC cases screen = 117; CRC cases control = 44; Goteborg 1994) and Nottingham trials (at 7.8 years follow-up CRC cases screen = 893; CRC cases control = 856; Nottingham 1996). It was suggested that the discrepancy in the number of CRC cases detected in the Minnesota trial (at 13 years follow-up CRC cases annual screen = 323; CRC cases biennial screen = 323; CRC cases control = 356; Minnesota 1993) may have occurred through chance and that this may then also be associated with an underestimation of CRC mortality in the screening groups (Towler 1998). However, it is interesting to note that the Minnesota trial was reporting at 13 years follow-up, in comparison to the much shorter reported length of follow-up for the other trials. Indeed, in a later publication of the Funen trial, the screening and control groups were almost identical in identified CRC cases (at 10 years follow-up CRC cases screen = 481; CRC cases control = 483; Funen 1996).

With further follow-up, the decreasing number of CRC cases occurring over time between the screening and control groups was evident in most of the included trials. In the Funen trial, the number of CRC cases was only slightly higher in the screening groups in comparison to the control groups (see Table 6). The Minnesota (CRC cases annual screen = 417; CRC cases biennial screen = 435), Goteborg and Nottingham trials all reported a lower number of CRC cases in comparison to the control groups. This suggests that other factors, rather than chance (see Lang 1994; Church 1997; Ederer 1997), may have contributed to the reported lower number of CRC cases in the screening groups. There is support for the reduction in the incidence of colorectal cancer following colonoscopic polypectomy (Citarda 2001; New York 1993). The reduced number of CRC cases for the screening groups most likely reflects the efficacy of colonoscopic polypectomy in preventing adenomas from developing into CRC. Indeed, two of the trials (Funen, Goteborg) reported a very large number of identified adenomas in the screening groups in comparison to the control groups (Funen: screen group = 481 adenomas, control group = 174 adenomas, Kronborg 1989; Goteborg: screen group = 419 adenomas, control group = 51 adenomas, Goteborg 1994).

Table 6: Number of CRC cases and incidence rate of CRC cases for screening and control groups in included trials.

	No. CRC Cases		Incidence rate	
RCTs	***Screen***	***Control***	***Screen***	***Control***
Nottingham	1268/76466	1283/76384	1.51/1000py	1.53/1000py
Funen	889/30967	874/30966	2.06/1000py	2.02/1000py
Goteborg	252/34144	300/34164	1.53/1000py	1.60/1000py
Minnesota	852/31157	507/15394	32-33/1000	39/1000

As would be expected with screening, all four trials reported more early stage colorectal cancers (Dukes A) and less late stage colorectal cancers (Dukes D or Dukes C and D) in the screening groups compared with the control groups (see Table 7). This favourable shift in colorectal cancer staging occurred across the trials, although the proportion of cancers that were actually screen-detected (e.g. excluding interval cancers, re screening and cancers detected in non-responders to the screening invitation) was fairly low (23% to 46% for Dukes A reported in two of the included trials) (Funen 1996; Nottingham 1996).

Table 7: Stage of CRC diagnosis for screening and control groups in included trials.

	Screening Grp				Control Grp			
RCTs	***A***	***B***	***C***	***D***	***A***	***B***	***C***	***D***
Nottingham	20%	32%	24%	22%	11%	33%	31%	21%
Funen	22%	34%	19%	20%	11%	37%	23%	24%
Goteborg	26%	28%	32%	14%	9%	34%	21%	17%
Minnesota-A	30%	29%	23%	9%	22%	31%	21%	17%
Minnesota-B	27%	26%	26%	11%	-	-	-	-

Further investigation rates

Rates of further diagnostic evaluation (e.g. colonoscopy or sigmoidoscopy, completion rates for colonoscopy, etc) were reported for all of the included trials. The main investigation was colonoscopy (three of the trials), with only the Goteborg trial using flexible sigmoidoscopy and double-contrast barium enema (DCBE). Around 9 in 10 patients with a positive FOB had further testing. In the

Funen trial, 93% of participants with a positive Haemoccult result attended at least one colonoscopy examination. In the Minnesota trial, 83% of the annual screening group and 84% of the biennial group returning a positive FOBT result underwent a colonoscopy or a flexible sigmoidoscopy and double-contrast barium enema. In the Nottingham trial 87% of participants with a positive result underwent either colonoscopy, double contrast barium enema or both. In the Goteborg trial, 92% of participants with a positive test attended flexible sigmoidoscopy and a double contrast barium enema.

In the two trials that used colonoscopy as the primary means of further investigation (the Goteborg trial primarily used flexible sigmoidoscopy) and reported complications of the procedure, the rate of perforation during colonoscopy is approximately 1 in 1,400 (9/13,720 = 0.0007). Adverse outcomes were reported in detail for 3 of the trials (Goteborg, Minnesota, Nottingham). The Goteborg trial reported adverse outcomes for both flexible sigmoidoscopy and colonoscopy. In this trial, 3 participants (out of 2,108 participants) who received follow-up by flexible sigmoidoscopy had perforations of the sigmoid colon (Goteborg 1996). All three participants recovered without complications. Three complications (out of only 190 procedures) were also reported for participants undergoing colonoscopy in the Goteborg trial (two perforations and one bleeding complication; perforation detected at polypectomy, perforation of sigmoid colon due to colonoscope and bleeding detected 12 days after polypectomy). In the Minnesota trial, of the 12,246 colonoscopies performed at the University of Minnesota hospital there were four perforations of the colon (all requiring surgery) and 11 serious bleeding (3 requiring surgery) complications (Minnesota 1993). The Nottingham randomised trial reported that there were seven complications (out of 1,474 procedures) associated with colonoscopy (five perforations, one major bleed, one snare entrapment) (Nottingham 1999). Six of these complications required surgery although none of these patients died from the colonoscopy complications.

The cumulative risk of being invited for further investigation (either colonoscopy or flexible-sigmoidoscopy) following a positive FOBT was 2.6% (1,977/76,466) for the Nottingham trial, 5.3% (1,647/30,762) for the Funen trial and 6.4% (2,180/34,144) for the Goteborg trial. The total number of positive screening tests is not reported for the Minnesota trial. However, the number of positive screening tests that were followed by an adequate examination (either colonoscopy or flexible sigmoidoscopy and DCBE) were reported as 8,663 for the annual screening group and 5,170 for the biennial screening group (Minnesota 2000). Based on the reported compliance rate for further investigation (annual = 83%; biennial = 84%), the estimated cumulative risk of being invited for further investigation in the Minnesota trial was 65% for the annual group (8,663/15,570 X 1.17) and 38% for the biennial group (5,170/15,587 X 1.16).

DISCUSSION

The evidence from the randomised controlled trials included in this review, indicates that screening with Haemoccult reduces mortality from colorectal cancer. Based on all randomised participants, the reduction of colorectal cancer mortality from inviting participants to repeat screening is 16% (RR 0.84, CI: 0.78-0.90). Although the trials varied in the selection and age of their study populations, screening intervals, conditions of Haemoccult testing and slide processing, length of follow-up and attendance for screening, the relative reduction in colorectal cancer mortality with screening is consistent across the trials.

The effectiveness of a screening programme depends on the accuracy of the screening test used to detect the condition. The majority of trials reported that the positive predictive value (PPV) of Haemoccult for colorectal cancer was fairly low (see Table 5), suggesting that over 80% of all positive tests were false-positives. These false-positive participants would have been encouraged to attend a further diagnostic investigation, which may have resulted in some negative consequences (e.g. stress, anxiety, other psychosocial consequences) and a small chance of significant adverse consequences from the diagnostic test (e.g. risk of bleeding, bowel perforation or even death). Although this must also be tempered by the PPV for adenomas (1 cm or over), which was higher in comparison to the colorectal cancer PPV. Removal of adenomas identified at screening may also reduce the likelihood of the development of colorectal cancer in the future (New York 1993; Citarda 2001), although this has not been definitively demonstrated.

A criticism of the previous Cochrane review was that it did not include an analysis of all-cause mortality. The all-cause mortality from four of the randomised trials (Funen, Goteborg, Minnesota and Nottingham) combined showed no difference between the screening and control groups (RR 1.00, CI: 0.99-1.03). Although the expectation that all-cause mortality would be decreased as a result of a decrease in mortality in the intervention group (Black 2002) this would only be so for diseases that have a significant impact on overall mortality. A major limitation of using all-cause mortality as an endpoint in cancer screening trials is that it is poorly powered as the intervention is targeted to a disease that causes only a small proportion of overall deaths. A complete analysis of the specific reasons for death (e.g. coronary heart disease, stroke, car accidents, etc) contributing to the all-cause mortality would help to determine if people who have survived colorectal cancer die of other causes several (or more years) later.

The estimate of mortality reduction from the updated randomised and controlled Haemoccult trials is consistent. Haemoccult screening is likely to be of benefit in reducing colorectal cancer mortality for particular population groups (e.g. older adults given the increased incidence of colorectal cancer with age). The included trials also indicated that there was a general shift towards identifying colorectal cancer in the earlier stages within the screen-

ing groups (e.g. Duke's Stage A) in comparison to the control groups. However, this is to be expected, given that screening studies would identify earlier stage lesions due to lead and length time biases. Other benefits of screening that were not explored in detail include the reduction in colorectal cancer incidence through detection and removal of colorectal adenomas, and potentially, less invasive treatment of identified early-stage colorectal cancers.

Alternative CRC screening modalities to FOBT are currently under investigation or in use. The suggested improved accuracy and patient acceptance of immunochemical FOBT (FIT) have been forwarded as reasons for adopting FIT over guaiac FOBT for population screening (Guittet 2009; Federici 2005; Netherlands 2008). Ongoing trials of flexible sigmoidoscopy (FS), either alone or in combination with FOBT/FIT to reduce CRC mortality have also yielded promising findings (Atkin 2010; Hoff 2009; Weissfeld 2005; Netherlands 2010; Segnan 2005) with more definitive results expected in several years.

AUTHORS' CONCLUSIONS

Implications for practice

Who would be likely to benefit from colorectal cancer screening using Haemoccult? Assuming a constant reduction in relative risk, the mortality benefit of screening is greatest in populations at greater risk of colorectal cancer death whilst the harmful effects of screening are likely to be independent of this risk (Glasziou 1995). Indeed, increasing screening benefit with increasing population risk of colorectal cancer death was observed in the screening trials.

The reduction in the relative risk of colorectal cancer death with screening needs to be interpreted for its benefit in the overall population where there are differing baseline risks for colorectal cancer. For example, the risk of colorectal cancer increases markedly with age and also in people who have a family history of CRC (Weitz 2005; Cappell 2005). However, people who have a genetic disposition, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), have an greatly increased risk of developing colorectal cancer (Faivre 2002; Lynch 2000). These individuals would not benefit from population screening, but are likely to benefit from specific monitoring of their conditions through dedicated genetic services (Bliss 2004).

Implications for research

Several important areas require further research. First, there is relatively little information currently available concerning the information needs and psychosocial consequences of screening for colorectal cancer. Specific research regarding the best method to provide relevant, high-quality information about the benefits, risks and potential consequences of screening is important to allow people to make and informed choice if they are offered screening. Moreover, the specific information needs of people regarding the type of information that is most relevant to their decision and how best to communicate the possible risks associated with colorectal screening also need to be addressed. Second, there is limited research on patient acceptance of colorectal cancer screening or on how best to involve particular sections of the community, who are often under-represented in other screening activities, in potential colorectal cancer screening programmes. Thirdly, the accuracy of other variants of the faecal occult blood test (e.g. RHNA) for colorectal cancer screening also require further investigation, particularly in comparison to existing tests.

Estimated screening benefit for potential screening populations should guide health policy decisions about to whom screening can be offered. For example, in England and Wales in 2004, the cumulative 10 year mortality from colorectal cancer in males for the decades beginning 40, 50 and 60 are respectively 5, 22 and 70 per 10,000 individuals (ONS 2005). If offering screening reduced this mortality from colorectal cancer by 16%, then the reduction in CRC deaths over the following 10 years for each of these age groups would be 0.8, 3.5 and 11.2 respectively, per 10,000 invited. This somewhat overestimates the benefits of CRC screening, as some of the mortality relates to those diagnosed prior to that decade (ONS 2004). However, it is also an underestimate for those who regularly attend CRC screening. If we use the mortality reduction of 25% estimated for those who regularly attend screening, the reduction in CRC mortality over 10 years for those aged 40, 50 and 60 would be 1.25, 5.5 and 17.5 per 10,000 respectively. Although the relative risk reduction is held to be constant across the trials, greatest reduction in CRC deaths that could be achieved by CRC screening is dependent on the advancing age of the individual (although, given the lack of an effect for all-cause mortality, an increase in life years may not be observed). Hence targeting and monitoring of population programs also requires attention.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Funen 1996

Methods	Random allocation of individuals identified from a population register of Funen county (central randomised procedure adjusted for married couples who were allocated to the same group) Analysis by intention to screen (treat) 6 persons lost to follow-up Blinded standardised assessment of CRC mortality
Participants	Inhabitants of Funen (Denmark) aged 45-75 years Screen group: Biennial group = 30,967; Control group = 30,966 Trial group comparability: age and sex similar for both groups
Interventions	Biennial Hemoccult Screening group Vs Control group Hemoccult-II not rehydrated Screening and follow-up: August 1985-1995; 5 screening rounds
Outcomes	Colorectal cancer mortality at 10 years follow-up Compliance with screening = 66.8% attended first round of screening, 45.9% (68.7% of first round participants) completed all 5 screening rounds Hemoccult-II sensitivity for CRC: 55% Positive predictive value for CRC: 17% in first round of screening; 10% at final round of screening 96.3% positive FOBt attended diagnostic follow-up (83.9% complete COL, 6.6% incomplete COL+DCBE, 5.9% incomplete colorectal exam) No information on number of COL performed or complications of COL Number of CRC cases: Screening group 481 (1.71/1000), Control group 483 (1.72/1000) Number of CRC deaths: Screening group 182 (0.65/1000), Control group 230 (0.82/1000) Number of deaths from CRC and complications of treatment: Screening group 205 (0.73/1000), Control group 249 (0.89/1000) Deaths from all causes: Screening group 6228 (22.09/1000), Control group 6303 (22.40/1000) Proportion of Dukes A: Screening group 26.6% (46% positive FOBt, 5% before invitation to screen, 20% non-responders, 30% interval cancers) and Control group 22.3% Mortality reduction: 16%
Notes	6 people moved away from Denmark, therefore, death certificates not available (uncertain if these 6 people died) Survival rate highest in patients with screen-detected CRC than in controls (log-rank test p<0.01)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Funen 2002

Methods	See Funen 1996
Participants	See Funen 1996
Interventions	See Funen 1996
Outcomes	Colorectal cancer mortality at 13 years follow-up male/female ratio decrease from 0.92 to 0.81 Mean age increased from 59.8 yrs to 70.0 yrs Compliance with screening = 1st invitation 67%; 2nd to 7th invitations = 92-94% Proportion of positive FOBt ranged from 0.8% to 3.8%; cumulative risk of positive FOBt at least once 5.1% (1,559/30,762) 94.1% follow-up (1,467/1,599) of persons with positive FOBt; complete COL ranged from 81.6 to 89. 3% (over the 7 screening rounds) No mortality from COL in screening group Number of CRC cases: Screening group 649 (1.84/1000py), Control group 637 (1.81/1000py) Number of CRC deaths: Screening group 255 (0.82/1000py), Control group 310 (0.88/1000py) Deaths from all causes: Screening group 8,732 (24.78/1000py), Control group 8,724 (24.80/1000) Mortality reduction: 15% for CRC mortality (0.73-1.00)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Funen 2004

Methods	See Funen 1996
Participants	See Funen 1996
Interventions	See Funen 1996 All Ss followed-up until death or Aug 2002 (17 years after start of study); by 9th screening round, 19,654 Ss in Screen group still alive, 9,367 were invited as participated in previous 8 rounds and not diagnosed with colorectal neoplasia (incl 41 Ss unfit for COL)
Outcomes	Colorectal cancer mortality at 17 years Mean age increased from 59.8 yrs to 73.0 yrs (mean age accepting invitation less than mean age for those declining invitation); male/female ratio decrease from 0.92 to 0.78 Compliance with screening = 1st invitation 67%; 2nd to 9th invitations = 91% Hemoccult sensitivity = 55% Proportion of positive FOBt ranged from 0.9% to 3.8%; cumulative risk of positive FOBt at least once 5.7% (1,766/30,762) 93.2% follow-up (1,647/1,766) of persons with positive FOBt; complete COL in 89% Positive predictive value for adenoma = 10mm: 31.6% 1st screening, 22.1% 9th screening Positive predictive value for CRC: 17.2% 1st screening, 16.5% 9th screening

Funen 2004 (*Continued*)

	Number of CRC cases: Screening group 889 (2.06/1000py), Control group 874 (2.02/1000py) Number of CRC deaths: Screening group 362 (0.84/1000), Control group 431 (1.00/1000) Number of deaths from CRC and complications of treatment: Screening group 427 (0.99/1000), Control group 479 (1.10/1000) Deaths from all causes: Screening group 12,205 (28.3/1000), Control group 12,248 (28.4/1000) Proportion of Dukes A: Screening group 36% (72/199 with positive Hemoccult-II), if all Ss in the screening group included 18% (162/889); Control group 11% (99/874) Mortality reduction: 16% for CRC mortality; 11% for CRC morality including complications from treatment
Notes	Incidence of CRC similar in the two groups; mortality rates almost identical in the screening and control groups Mortality from CRC less in screening group, but not statistically significant when post-op complications included Risk of death decreased with increasing number of screening rounds (after 9 rounds, RR of death from CRC <0.60 compared with risk in controls); 43% reduction in mortality after 9 screening rounds, 42% after 7 screening rounds, 40% after 5 screening rounds Interval cancer cases better prognosis than controls (survival curves)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Goteborg 1994

Methods	Random allocation of individuals of Goteborg born between 1918 and 1931 (3 cohorts depending on time of birth; 1918-1922, 1923-1927 and 1928-1931; the time between inclusion of the 1st and 2nd cohorts was 5 years, the time between the 2nd and 3rd cohorts was 4 years) No indication if intention to screen used for analysis 713 persons in the Screen group died before the second test was sent out and 58 could not be located (Total = 771) 593 persons in the Control group died before the second test was sent out and 29 could not be located (Total = 622) CRC mortality determined by one physician not involved in trial (blinded assessment)
Participants	All 68,308 inhabitants of Goteborg (Sweden) aged 60-64 years Screen group = 34,144; Control group = 34,164 Trial group comparability: age balance demonstrated (no information on sex or other variables)
Interventions	Hemoccult II screening group (two screens) Vs Control group All Hemoccult slides hydrated except for participants born between Jan 1918 - July 1920 during the first screening Screening commenced in 1982; ; 2nd screen performed 16-24 months after 1st (mean 2nd screen = 20 months, after first screen)

Goteborg 1994 (*Continued*)

Outcomes	Colorectal cancer mortality at 8.5 years (range 2 to 9 years) Compliance with screening = 63% 1st screening, 59% 2nd screening Hemoccult sensitivity 82% (based on interval between negative test and re screening or within two years of final screening); Specificity NR Positive predictive value: NR 85% positive FOBt from 1st screening (or positive retest in 3rd cohort) attended diagnostic follow-up (COL), 5% received SIG only and 10% refused. 88% positive FOBt from re screening attended diagnostic follow-up (SIG, PROCT, DCBE), 4% received SIG only and 8% refused No information on complications of COL (see Kewenter et al., 1996) Number of CRC cases: Screening group 117 (2.2/1000 in 1st screening, 3.8/1000 for all Ss, 1.5/1000 Ss in 1st and re screening); Control group 44 (1.29/1000) Number of CRC deaths: No information provided Deaths from all causes: No information provided Proportion of Dukes A: Screening group 25.6% (29 screen-detected, 1 non-responder) and Control group 9.1% Mortality reduction: NR
Notes	Authors report 60% compliance for second screening, however, actual figure 58.5% (19,991/34,144), unless second compliance calculated on withdrawals from screening group in study (19,1991/33,431 = 60%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Goteborg 1996

Methods	As Goteborg 1994
Participants	As Goteborg 1994
Interventions	As Goteborg 1994 (reporting diagnostic and surgical complications in screening trial)
Outcomes	FSig = 2,108 (repeated in 2% due to unclean intestine); 554 polyps in 413 Ss removed 3 perforated sigmoid colon (0.5% of all polypectomies/0.7% all Ss); no bleeding events reported DCBE = 1,987 of 2,108 (94.3%) underwent exam; 3% repeat examination; no complications reported COL = 190; COL performed to remove possible adenomas in 113 cases identified at DCBE 3 complications of COL; 3 perforations Laparotomy = CRC removed in 79 cases; all Ss treated without any mortality (3 Ss required additional LAP; 1 post-op bleeding, 1 perforation causing peritonitis, 1 unknown but suspected peritonitis) 13 adenomas removed by LAP (endoscopic removal considered inappropriate)
Notes	

Risk of bias

Goteborg 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Goteborg 2005

Methods	As Goteborg 1994
Participants	As Goteborg 1994
Interventions	As Goteborg 1994
Outcomes	Colorectal cancer mortality at 15.5 years (range 11 to 19.4 years) Compliance with screening = 63% 1st screening, 70% at least one screen 92% (2009 persons) attended diagnostic follow-up (SIG, DCBE) Number of CRC cases: Screening group 721 (104 screen detected); Control group 754 Number of CRC deaths: Screen group 252; Control group 300 Deaths from all causes: Screening group 10591; Control group 10432 Mortality reduction: 16% (RR 0.84, CI 0.67-0.99).
Notes	Unpublished information from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Goteborg 2008

Methods	As Goteborg 1994
Participants	As Goteborg 1994
Interventions	As Goteborg 1994
Outcomes	Colorectal cancer mortality at mean follow-up time of 15 years and 9 months (range 11 years and 3 months to 19 years and 5 months) from first invitation; mean follow-up time of 8 years and 8 months (range 6 years and 7 months to 13 years and 5 months) since last screening occasion Compliance with screening = 61.8% in total (62.5% prevalence round, 59.9% 1st screening round, 63. 9% 2nd round, 47.2% completed all screening rounds) Hemoccult sensitivity NR; Hemoccult specificity NR. Positive Predictive Value for CRC: 4.8% total (5.9% prevalence screen, 4.1% 1st screen, 4.1% 2nd screen) 86.7% positive FOBt overall attended complete diagnostic follow-up which included FSig and DCBE (87.3% prevalence round, 89.7% 1st screening round, 81.1% 2nd round) No information on complications of diagnostic follow-up.

Goteborg 2008 (*Continued*)

	Number of CRC cases: Screening group = 721 (104 screen detected, 413 at follow-up, 204 non-participants); Control group = 754 Number of CRC deaths: Screening group = 252 (mortality rate = 0.53 per 1000 person-years), Control group = 300 (mortality rate = 0.64 per 1000 person-years) Deaths from all-causes: Screening group = 10591 (mortality rate = 22.48 per 1000 person-years), Control group = 10432 (mortality rate = 22.10 per 1000 person-years); Mortality ratio: RR 1.02, CI 0.99 to 1.06 Mortality reduction: 16% (RR 0.84, CI 0.71 to 0.99). Comparison between accepting screening once versus Control: 24% (RR 0.76, CI 0.63 to 0.92)
Notes	Due to changes in the classification of 'positive FOBt' (see p1031) number of positive FOBt tests differ between 2008 publication and 1994 publication (1994 = 942 positive FOBt in prevalence round; 2008 = 801 positive FOBt in prevalence round; also, 1994 = 1019 positive FOBt in 1st screening round; 2008 = 846 positive FOBt in 1st screening round) Number of CRC cases from positive test same in both publications, however, number of adenomas10 mm or above differ (1994 = 129 Ss with adenomas 10 mm or above in prevalence round; 2008 = 114 Ss with adenomas 10 mm or above in prevalence round)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Minnesota 1993

Methods	Individual random allocation of volunteers (stratified by age, sex and place of residence) Analysis by intention to screen No loss to follow-up nor exclusions - see comments Blinded, standardised assessment of CRC mortality
Participants	Volunteers recruited from the American Cancer Society (and fraternal), veterans and employee groups in the Minnesota area. Aged 50 to 80 years. Screen groups: Annual group (Agrp) = 15,570; Biennial group (Bgrp) = 15,587; Control group (Cgrp) = 15,394; Total = 46,551 Trial group comparability: age, sex and place of residence similar for all groups
Interventions	Annual and Biennial Hemoccult screening groups Vs single Control group Hemoccult 82.5% rehydrated (rehydrated used between 1977 to 1982, then 1986 to 1992; not rehydrated used between 1976 to 1981) Screening: 1975-1982, and 1986-1992
Outcomes	Colorectal cancer mortality at 13 years follow-up Compliance with screening = Agrp 75.2% (all 46.2%), Bgrp 78.4% (all 59.7%); 90% of each group completed at least one screen Hemoccult sensitivity for CRC: 92.2% and specificity 90.4% for rehydrated; sensitivity 80.8% and specificity 97.7% for not rehydrated Positive predictive value: 9.8% for rehydration and 2.4% for not rehydrated slides 75% positive FOBt attended diagnostic follow-up (Uni Minn). 20% own physician, 5% declined

Minnesota 1993 (*Continued*)

	12,246 COL at Uni Minn; 4 perforation (all required surgery) and 11 serious bleeding (3 required surgery) Number of CRC cases: Agrp 323 (23/1000), Bgrp 323 (23/1000), Cgrp 356 (26/1000) Number of CRC deaths: Agrp 82 (5.88/1000), Bgrp 117 (8.33/1000), Cgrp 121 (8.83/1000) Deaths from all causes: Agrp 3361 (216/1000), Bgrp 3396 (218/1000), Cgrp 3340 (216/1000) Proportion of Dukes A: Agrp 30.2%, Bgrp 26.6% and Cgrp 22.3% Mortality reduction: 33% for Agrp; 6% for Bgrp
Notes	Previous review: reported no loss to follow-up nor exclusions, however, Church et al (1991) report 299 Ss withdrew

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Minnesota 1999

Methods	See Mandel et al 1993 (Update of Minnesota study)
Participants	See Mandel et al 1993
Interventions	See Mandel et al 1993 All Ss followed-up until death or Aug 2002 (17 years after start of study); by 9th screening round, 19,654 Ss in Screen group still alive, 9,367 were invited as participated in previous 8 rounds and not diagnosed with colorectal neoplasia (including 41 Ss unfit for COL)
Outcomes	Colorectal cancer mortality at 18 years follow-up Compliance with screening = Agrp 75%, Bgrp 78% Agrp average of 3.7 screens in Phase I and 4.0 screens in Phase II; Bgrp average of 2.3 screens in Phase I and 2.1 screens in Phase II 95% Ss with positive screen received diagnostic follow-up (5% declined to consult a physician); Agrp 83% and Bgrp 84% underwent complete COL or FSIG+DCBE Number of CRC deaths: Agrp 121 (9.46/1000), Bgrp 148 (11.19/1000), Cgrp 121 (14.09/1000) Deaths from all causes: Agrp 5236 (342/1000), Bgrp 5213 (340/1000), Cgrp 5186 (343/1000) Cumulative CRC mortality ratio: Agrp 0.67 (CI: 0.51-0.83); Bgrp 0.79 (CI: 0.62-0.97), Cgrp 1.00 Duke's stage D: Agrp 47% fewer than control; Bgrp 32% fewer than control Mortality reduction: 33% Agrp, 21% Bgrp
Notes	Survival rates for Duke's stage: A = 94.3%, B = 84.4%, C = 56.6%, D = 2.5%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Minnesota 2000

Methods	See Mandel et al 1993 and 1999 (Update of Minnesota study) Follow-up for vital statistics complete for 91.3% (Agrp), 91.7% (Bgrp) and 91.2% (Cgrp); 95% complete for all groups through to Year 17 Death certificates missing for 3 of the 18,873 people who were known to have died during 18 year follow-up
Participants	See Mandel et al 1993 and 1999
Interventions	See Mandel et al 1993 and 1999
Outcomes	Colorectal cancer incidence at 18 years follow-up Number of CRC cases: Agrp 417 (32/1000), Bgrp 435 (33/1000), Cgrp 507 (39/1000) Agrp PPV for CRC: ranged from 0.87% for one positive slide and 4.53% for six slides Bgrp PPV for CRC: ranged from 1.12% for one positive slide and 6.13% for six slides Agrp PPV for adenomatous polyps =1cm: ranged from 5.99% for one positive slide and 7.87% for six slides Bgrp PPV for adenomatous polyps =1cm: ranged from 6.86% for one positive slide and 10.08% for six slides Mortality reduction: see Mandel et al 1999
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nottingham 1996

Methods	Central randomisation of households identified from GP records (stratified by size, sex and average age of eligible members) Analysis by intention to screen (however, authors report that Ss lost to follow-up excluded from analysis) 1.7% (2,599) of randomised Ss lost to follow-up Blinded, standardised assessment for CRC mortality and other outcomes
Participants	Individuals living in the Nottingham area aged 45-74 years (50-74 years main trial, 45-74 years pilot study); 1053 (506 screen group, 547 control group) over 75 years at entry of study Screen group: 76,466 (75,253 offered screening after exclusion); Control group: 76,384 (74, 998 after exclusion) Trial group compatibility: age and sex similar for both groups
Interventions	Biennial Haemoccult screening group Vs Control group Haemoccult not rehydrated Recruitment Feb 1985-Jan 1991 (main study), Feb 1981-June 1983 (pilot study); Screening ceased Feb 1995; follow-up to end-June 1995

Nottingham 1996 (*Continued*)

Outcomes	Colorectal cancer screening mortality at median 7.8 years (range 4.5-14.5 years) Compliance with screening: 59.6% completed at least one screen (38.2% completed all FOBt offered, between 3 to 6 screens) Haemoccult sensitivity for CRC: 53.6% (Robinson et al 95) Positive predictive value: 1st invite = 47.1%, later invite to 1st refusers = 54.5% (first screening); Within 27 mnths = 44.8%, after 27 mnths = 42.8% (re screening); 46.2% average 2.1% (960) Ss needed full investigation after first screen; 1.2% (1090) FOB tests positive after re screening Detection rates for adenomas and CRC higher for over 65 (7.7 vs 4.4/1000 and 3.4 vs 1.1/1000); also higher in men (7.2 vs 3.8/1000 and 2.3 vs 1.5/1000) 1778 screen group underwent COL (4% of FOBt Ss with one+ screen) one 1+ occasions) 74% (174/236) of CRC detected at screening in rectum or sigmoid colon Number of CRC cases: Screening group 893; 236 FOBt, 249 interval, 400 non-responders, 8 endoscopic adenoma follow-up (1.49 per 1000 person-years); Control group 856 (1.44 per 1000 person-years) Number of CRC deaths: Screening group verified 360 (0.60/1000py), Control group verified 420 (0.70/1000py); Screening group certified 350 (0.59/1000py), Control group 398 (0.67/1000py) Deaths from all causes: 12,624 (21.1/1000py), Control group 12,515 (21.0/1000py) Proportion of Dukes A: Screening group 20% (42 1st invite, 6 later invite, 49 rescreen, 39 interval, 3 adenoma follow-up) and Control group 11% (95) Mortality reduction: 15% reduction in cumulative CRC morality in screening group (OR=0.85, CI 0.74-0.98; p=0.026)
Notes	4.3% more cancers diagnosed in the screening group in comparison to control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nottingham 1999

Methods	See Hardcastle et al 1996 (Update of Nottingham study - primarily concerning risks associated with colonoscopy after positive CRC screening result)
Participants	See Hardcastle et al 1996
Interventions	See Hardcastle et al 1996
Outcomes	1778 people (4% of those accepting screening at least once) underwent colonic investigation at least once (1474 colonoscopies and 738 DCBEs were performed). 960 people (2.1%) required colonic investigation after first screen. 236 CRC cases and 249 interval CRC cases in screen group (400 CRC cases in non-participants in the screen group). 856 CRC cases in the control group. 13 interval cancers following a positive test (two investigated by COL, 6 DCBE and 5 refusals). Sensitivity of colonic investigation estimated as 96.7% (236/244). Eight interval cancers (A=0, B=1, C=3, D=4), none presented in first year, 6 in the second year and one

Nottingham 1999 (*Continued*)

	in the third year (remaining case presented 13 years following positive test). COL missed two cancers - sigmoid colon and caecum. 6 DCBE missed cancers proximal to hepatic flexure. Seven (7/1474 = 0.5%) complications associated with COL (5 perforations, one major bleed, one snare entrapment). Six required surgical intervention. No COL related deaths (no patients died within 30 days of COL who were not being treated for CRC). No DCBE complications. Five patients died within 30 days of surgery (days 0, 1, 4, 9, 14) for screen detected CRC (A=0, B=1, C= 2, D=4)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nottingham 2002

Methods	See Hardcastle et al 1996 (Update of Nottingham study) Standard intention-to-treat analysis used for controls (incidence and mortality) Cuzick et al 1997 (allowing for the differences in underlying rates of acceptors and non-acceptors of screening to produce less biased estimate of RR) method used to provide estimate of CRC mortality in those accepting the first screening test relative to controls 547 (0.4% both groups) could not be located by ONS or emigrated, therefore, excluded from mortality analysis
Participants	See Hardcastle et al 1996 Screen group: 76,466 (76,224 after loss to follow-up); Control group: 76,384 (76, 079 after exclusion); NOTE: different to previous figures reported in Hardcastle et al 1996
Interventions	See Hardcastle et al 1996 Person years in the screen and control groups calculated from date of study entry to 30 June 1999 or death
Outcomes	Colorectal cancer mortality at median follow-up 11.7 years (range 8.4 to 18.4 years) Compliance 57% 1,977 Ss in screen group tested positive at least once (cumulative risk 2.6% of having positive test) 73% (1,439) underwent COL, remaining undergoing other investigations (e.g. DCBE); cumulative proportion of Ss undergoing one COL as follow-up after positive FOBt was 1.9% Report possible cardiovascular complication of COL, rate higher in Ss undergoing COL following positive FOBt (6.4/1000py) than controls (5.9/1000py), but non-significant Number of CRC cases: Screening group 1,268 (1.51 per 1000py); Control group 1,283 (1.53 per 1000py) Number of verified CRC deaths: Screening group 593 (0.70/1000py), Control group verified 684 (0.81/ 1000py) Deaths from all causes: 20,421 (24.18/1000py), Control group 20,336 (24.11/1000py) Mortality reduction: 13% (RR 0.87; CI 0.78-0.97, p = 0.01)
Notes	

Nottingham 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

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

Study	Reason for exclusion
Almpoea 2004	One-time non-randomised FOB test screening
Beijing 2004	Non-randomised study
Burgundy 2004	Non-randomised study
California 1993	Case-control study
Calvados 1996	Non-randomised mass screening programme
Florence 1997	Case-control study
Guildford 2001	Case-control study
Italy 2010	No control group
Japan 1995	Case-control study
Jiashan 2003	One-time FOB test
Milan 1999	Nested case-control study
Netherlands 2008	No control group
Netherlands 2009	No control group
Netherlands 2010	No control group
New York 1993	Non-randomised study
Saarland 1993	Case-control study
Turin 2010	No control group

(*Continued*)

Tuscany 2008	Non-randomised mass screening programme
Washington 1995	Case-control study

DATA AND ANALYSES

Comparison 1. All Hemoccult Screening Groups Versus Control Groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Colorectal cancer mortality (Fixed)	4	329642	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.78, 0.90]
1.1 Randomised controlled trials	4	329642	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.78, 0.90]
2 Colorectal cancer mortality (Random)	4	329642	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.78, 0.90]
2.1 Randomised controlled trials	4	329642	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.78, 0.90]

Comparison 2. Biennial Only RCT Screening Groups Versus Control Groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Colorectal Cancer Mortality (Fixed)	3	245764	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.78, 0.92]
1.1 Randomised Controlled Trials	3	245764	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.78, 0.92]
2 Colorectal Cancer Mortality (Random)	3	245764	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.78, 0.92]
2.1 Randomised Controlled Trials	3	245764	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.78, 0.92]

Comparison 3. All-Cause Mortality Screening Groups Versus Control Groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (Fixed)	4	329642	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.99, 1.02]
1.1 Randomised controlled trials (Fixed)	4	329642	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.99, 1.02]
2 All-cause mortality (Random)	4	329642	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.99, 1.01]

Comparison 4. All-Cause Mortality Without CRC Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause without CRC (Fixed)	4	326616	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [1.00, 1.03]
2 All-cause without CRC (Random)	4	326616	Odds Ratio (M-H, Random, 95% CI)	1.01 [1.00, 1.03]

FEEDBACK

Comments from Dr. Hans-Hermann Dubben, 21 July 2009

Summary

Based on the numbers given in your tables, I came to the conclusion that all-cause mortality is higher in the screening group as compared to the control group. Colorectal cancer (CRCa) screening does more harm than benefit: for one life prolonged there are almost three lives shortened.

From calculations I performed *(available from the CCCG editorial office)* there is a statistically significant increase in all-cause mortality in the screening group (p = 0.03).

Furthermore, calculations of absolute risk reduction (Control-Screening) showed that Number needed to harm (NNH) is one in 287 in the screening group. Other-cause mortality is significantly increased, and finally for the colorectal cancer specific mortality my calculations showed that per one life that is prolonged (omitting one CRCa death) there are about 625/211 = 2.96 lives shortened.

I would be very grateful if you could help me to answer a few questions:

1.) Would it not be prudent now to emphasize that colorectal cancer screening can be detrimental
in terms of all-cause mortality, or even to warn against colorectal cancer screening?

2.) Is there a strong argument why to use the Peto odds ratio in your review?

3.) Was the choice of the Peto odds ratio done a priori before the data were evaluated?

Yours sincerely, Hans-Hermann Dubben

Reply

Dear Hans-Hermann Dubben,

Thank you for your interest in the review and for taking the time to contact us in regards to your query. We also appreciate that you sent your analysis of the data to enable us to respond to your query.

Unfortunately, and with all due respect sir, we suspect that your calculations are incorrect. You seem to have pooled the results of all four trials, however, your analysis indicates that you have included both of the screening arms of the Minnesota trial (annual and biennial screening). Therefore, unfortunately you have introduced confounding into the analysis in that you have included a greater number of deaths in the screening arms than the control arms (essentially 5 screening groups versus 4 screening groups). This is also the reason why we performed the meta-analysis of the trials.

We decided to user the Peto method a priori given that:

a) it is appropriate for trials in which trials have roughly an equal number of participants in both groups

b) the treatment effects are small (e.g. CRC mortality is approximately 2% of all-cause mortality).

Indeed, the Peto method was developed specifically for use in cancer where small effects are likely, yet very important.

I hope that I have answered your query satisfactorily and would also like to indicate that we will be updating the review towards the end of this year. Thank you again for your time.

Kind regards,

Paul Hewitson

Research Fellow

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WHAT'S NEW

Last assessed as up-to-date: 6 June 2010.

Date	Event	Description
30 November 2010	Feedback has been incorporated	Comments and replies inserted
7 June 2010	New search has been performed	Update to previous Cochrane review (updated search and inclusion of results from one published RCT)

HISTORY

Review first published: Issue 2, 1998

Date	Event	Description
1 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PH conducted the literature search, assessment of abstracts, critical appraisal and data extraction of identified articles, main analyses and writing of the report.

PG was an author of the original review and contributed to the assessment of abstracts, main analyses and writing of the updated review.

BT was the lead author of the original Cochrane report.

EW contributed to the critical appraisal and data extraction of identified articles and comments on the report.

LI was an author of the original review and provided comments on the updated review.

DECLARATIONS OF INTEREST

There are no other potential conflicts of interest relating to this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cancer Research UK, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mass Screening; *Occult Blood; Colorectal Neoplasms [*diagnosis; prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans