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Systematic review of the effectiveness of population screening for colorectal cancer

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Abstract

Aim To estimate the effectiveness of colorectal cancer screening with faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), and combinations of FOBT and FS in preventing colorectal cancer (CRC) deaths.

Method A systematic review was conducted examining randomised controlled trials (RCTs) published between 1997 and 2004 inclusive. A systematic search of Medline, Embase, Current Contents, and the Cochrane Library was undertaken. Studies that evaluated screening with FOBT, FS or combinations of FOBT and FS, were appraised. A meta-analysis of population-based trials of FOBT was conducted.

Results Four RCTs were identified that examined FOBT screening. The three trials that investigated guaiac-based FOBT found CRC mortality was reduced in the screening group. In the two population-based trials, the pooled relative risk was 0.86 (95%CI 0.79–0.93). A fourth RCT was identified, with shorter term follow-up, which considered FOBT screening combined with FS compared with FOBT alone. No significant reduction in CRC mortality was reported in this trial.

Conclusion There is high-quality evidence showing that guaiac-based FOBT screening reduces mortality from CRC. No such evidence exists for screening with FS either alone, or in combination with FOBT, but this should be re-evaluated once data become available from four large ongoing trials.

At present, there is no routine organised population screening for colorectal cancer (CRC) in New Zealand. Concerns about high rates of mortality[1] and morbidity[2] from CRC in New Zealand have led to calls for population screening for the disease.

Proposed methods include faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), and combinations of these. In order to update a literature review completed in New Zealand in 1998,[3,4] a systematic review was conducted of the evidence for the clinical effectiveness of population screening for CRC using FOBT, FS, and FOBT and FS combined.[5] This paper focuses on CRC mortality and incidence. Colonoscopy, double contrast barium enema, and computed tomographic (CT) colonoscopy have also been suggested as possible screening tests but were not considered in this review due to the absence of new randomised controlled trial (RCT) efficacy data since 1998.

Methods

Search strategy—A systematic search of Medline, Embase, Current Contents, and the Cochrane Library was conducted. Extended searching included the DARE and Health Technology Assessment databases, clinical trial and guideline resources, and references from retrieved publications. Searches were limited to material published from January 1997 to November 2004 inclusive.

Study selection—Studies were eligible for inclusion in the review if they were full reports of RCTs that compared the clinical effectiveness of FOBT screening with no screening. Studies evaluating other screening methods including FS, and combined FS and FOBT approaches, were also considered. When there was more than one version of the study, the version with the longer follow-up was used.

Data extraction and synthesis—Data relevant to study quality and statistical precision were extracted using design-relevant checklists.[6] Key data extracted included characteristics of the study population, intervention and control group, sample size (by study group), number of screening rounds, duration of follow-up, and management of patients who were screen positive.

Results data for CRC incidence and mortality risk ratios, and positive predictive values, were either obtained directly from the studies or derived from available information. An analysis of numbers needed to screen (NNS) to prevent one CRC death was based on an intention to screen basis, using the groups that subjects were originally randomised to, although the limitations of this measure are recognised.[7] Confidence intervals for the NNS were calculated using the method suggested by Altman for number needed to test.[8]

The most recently published data, examining the effectiveness of screening with FOBT in reducing CRC mortality from the population-based RCTs, were used to conduct a meta-analysis. As there was no suggestion of heterogeneity, a fixed effects model meta-analysis was undertaken, using Stata (version 7.0) software.[9]

Full details of search terms, sources, study selection, and appraisal methods are provided in the NZHTA report.[5]

Results

Efficacy of faecal occult blood screening—The current review identified four RCTs comparing FOBT screening with no screening. Three of these trials used the guaiac test Haemoccult/Haemoccult II. The other trial used an immunochemical test (reverse passive haemaggutination) plus a health questionnaire.[16] Study design details are included in Table 1.

After 18 years follow-up in the Minnesota RCT, CRC mortality was significantly reduced in the annual group (21% reduction) and the biennial group (17% reduction). CRC incidence in the annual and biennial screening groups was also significantly reduced in this trial, by 33% and 21% respectively (see Table 2).[10,11] After a median of 11.7 years follow-up in the Nottingham trial, a 13% reduction in CRC mortality was reported for those in the screening group compared to the control group.[12] However, there was no significant difference in CRC incidence between the screening and control groups (see Table 2).

After 17 years of screening (nine screening rounds) in the Funen-1 trial, CRC mortality was reduced by 16% in the screening group compared with the control group, although this was reduced to an 11% reduction when treatment complications were included (see Table 2).[13] This result was not statistically significant, in contrast to estimates at shorter follow-up periods, including 10 years.[14] Results at 14 years follow-up were of borderline significance.[15]

Pooling the most recent data from the Nottingham and Funen-1 trials (excluding treatment complications) estimated that screening reduced the risk of death from CRC by 14% [RR = 0.86 (95% CI 0.79-0.93)]. Adding the results for biennial screening from the Minnesota RCT[10] made no difference to the pooled rate ratio [RR = 0.85 (95% CI 0.79-0.92)]. There was no evidence of heterogeneity between studies using Cochran's Q test.

Table 1. Characteristics of trials of faecal occult blood screening with or without flexible sigmoidoscopy screening

Variables	Minnesota[10,11]	Nottingham[12]	Funen-1[13]	Jiashan[16]	Funen-2[20]
Study population	Minnesota, USA, volunteers aged 50-80 years	Nottingham, UK, aged 45-74 years	Funen, Denmark, aged 45-75 years	Jiashan County, China, aged ≥ 30 years	Funen, Denmark, aged 50-75 years
Intervention	Guaiac FOBT, predominantly rehydrated	Guaiac FOBT, unrehydrated	Guaiac FOBT, unrehydrated	Immunochemical FOBT(reverse passive haemagglutination test) plus structured health questionnaire	Once only Guaiac FOBT + FS
Control	Usual care	Usual care	Usual care	Not reported	FOBT alone
Study groups	Annual screen 15,570 Biennial screen 15,587 Control 15, 394	Biennial screen 76,466 Control 76,384	Biennial screen 30,967 Control 30,966	Once only screen 94,423 Control 97,838	Once only Intervention group 5495 Control 5483
Screening rounds	Annual group: 11 Biennial group: 6	≥3	9	1	1
Participation rate	First round: Annual group 90% Biennial group 89% Average compliance Annual 75% Biennial 75%	First round: 53% Overall (after re-inviting non-responders) 59%	First round: 67% Further rounds: 91-97%	One-off screen: 66.4%	FOBT +FS: 40% FOBT alone: 56%
Follow-up	18 years	Median 11.7 years	17 years	8 years	2-5 years
Management of positive screen	Colonoscopy	Colonoscopy	Review plus colonoscopy	Flexible sigmoidoscopy	Colonoscopy

The report of the Jiashan trial provided data that allowed for calculations of the relative risks for CRC incidence and cumulative mortality following screening with an immunochemical FOBT.[16] The only statistically significant result pertaining to incidence and mortality was a 32% reduction [RR = 0.68 (95% CI 0.54-0.87)] in mortality from rectal cancer in the screening group compared to the control group. Incidence of rectal cancer was not significantly reduced. In addition, for both colonic cancer and overall colorectal cancer, there was no significant reduction in mortality or incidence. This may reflect the fact that most screen positive participants underwent evaluation of only the distal part of the bowel, by flexible sigmoidoscopy. It was not clear whether an intention to treat analysis was used in this trial, nor whether cluster randomisation was taken into account. Overall results are presented in Table 2.

Efficacy of flexible sigmoidoscopy screening—No completed RCT was identified which evaluated the impact of flexible sigmoidoscopy (FS) on colorectal cancer incidence and mortality. However, three large multi-centre trials are currently underway, with two exploring one-time screening[17,18] and one exploring repeated screening.[19] Incidence and mortality data will not be available until at least 2008 for the two one-off screening trials, and not until 2010–2012 for the repeated screening trial.

Efficacy of flexible sigmoidoscopy screening and faecal occult blood testing combined—One RCT, the Funen-2 trial, reported limited CRC incidence and mortality data for 5495 persons registered for once-only FOBT and FS testing compared with 5483 persons receiving FOBT alone.[20]

At 24–62 months follow-up, 11 versus 14 persons died of CRC for combined versus FOBT-only groups (p value not reported), and the CRC incidence rate of those screened in the combined screening group was 3.6 compared to 5.9 per 1000 in the FOBT-only group (p=0.24). The predictive value of a positive test for CRC was 2.8% after FOBT followed by FS, and 5.4% after FOBT alone. Subjects and physicians were unaware of FOBT results before FS and the criteria for a positive test resulted in 18.6% of the combined screening subjects having a full colonic examination compared to 2.3% after a positive FOBT test. See Table 2 for overall results.

Table 2. Results of trials of faecal occult blood screening with or without flexible sigmoidoscopy screening

Variables	Minnesota[10,11]	Nottingham[12,28]	Funen-1[13]	Jiashan[16]	Funen-2[20]
CRC mortality: Effectiveness RR (95%CI)	Annual screening RR 0.67 (0.51–0.83) Biennial screening RR 0.79 (0.62–0.97)	0.87 (0.78–0.97)	CRC mortality (including treatment complications): 0.89 (0.78-1.01) CRC mortality alone: 0.84 (0.73–0.96)	0.85 (0.71–1.03)	0.78 (0.36–1.73)
NNS to avoid one CRC death (95% CI)	Annual screening: 268 (169 – 645) over 18 years Biennial screening: 499 (NNSH3740 - ∞ - NNSB234)[1] over 18 years	826 (470 – 3390) over 11.7 years	449 (250 – 2184) over 18 years	2778[2] over 8 years	1813 (NNSH812–∞–NNSB428)[1] over a range of 2–5 years
CRC incidence: Effectiveness RR (95%CI)	Annual screening: RR 0.79 (0.62–0.97) Biennial screening: RR 0.83 (0.73–0.94)	0.99 (0.92–1.07)	1.02 (0.93–1.12)	0.98 (0.86–1.13)	1.37 (0.88–2.15)
Positive predictive value for CRC	Annual screening: 0.87%- 4.53% Biennial screening: 1.12% (1 of 6 slides positive) 6.13% (6 of 6 slides positive)	First screen = 9.9% Later invitation to those who refused first screen = 17.1% Rescreen = 11.9%–13.3%	First screen = 17.2% Ninth screen = 16.5% Rounds 2-8 range = 5.2%-18.7%	FOBT + questionnaire = 0.66%	First and once-only screen FOBT+FS: 2.8% FOBT: 5.4%

1) NNSH number needed to screen (harm), NNSB number needed to screen (benefit)

2) Insufficient information for confidence interval calculation

Discussion

There was high-quality evidence that screening with the guaiac FOBT Haemoccult reduces mortality from CRC. However, the three trials examining this screening test had important differences in their design. FOBT rehydration was undertaken in most screening in the Minnesota trial, but not the Nottingham and Funen-1 trials.

Rehydration increases the proportion of positive tests (which decreases the positive predictive value) and the number of diagnostic work-ups escalates. A higher rate of participants undergoing diagnostic work-up (with removal of adenomas) may explain why follow-up papers from the Minnesota RCT report a reduction in incidence of CRC, compared to both the Nottingham and Funen-1 trials, which found no difference

in incidence of CRC between screening and control groups.[11] Nevertheless, test rehydration inflates screening costs, as well as increasing potential screening harms from the more invasive diagnostic tests.

Currently, rehydration of guaiac-based FOBTs is not recommended by major organisations such as the World Health Organization[21] and the American Gastroenterological Association,[22] or by the manufacturer.[23]

Another important difference was in the method of participant recruitment. Since both the Nottingham and Funen-1 studies used population-based sampling, their results are the most applicable to organised population screening programmes (the Minnesota study used a volunteer population). Of interest in this respect is that participation rates for at least one round in these population-based RCTs was between 59–67%. This was similar to the participation rate (66.4%) of the Jiashan trial, which also invited members of the general public. The Minnesota RCT participation rate was higher (89–90% for the first round).[5.]

Despite these differences, the three trials estimated reduced rates of CRC mortality in the screening groups, although CRC mortality was not significantly reduced after longer-term follow-up in the Funen-1 trial. Evidence from ongoing follow-up of the two trials in which screening has stopped (Minnesota and Nottingham) suggests that this mortality reduction has been sustained. However, CRC mortality was not significantly reduced after longer term follow up in the Funen-1 trial for the population to whom screening has continued to be offered; Kronborg et al suggest that this lessening of risk reduction is likely to be due to smaller numbers of subjects being screened as the number of screening rounds increases.[13]

Pooled estimates of the two population based trials examining guaiac FOBT (Nottingham and Funen-1) or the three guaiac based RCTs (Minnesota, Nottingham, and Funen-1) suggests that screening resulted in significantly reduced colorectal cancer mortality. These results are similar to those found by Towler et al[24] who estimated a 16% reduction in mortality from colorectal cancer in a meta-analysis of earlier results. The Towler meta-analysis included the Minnesota, Nottingham, and Funen-1 trials (though with shorter-term follow-up) plus data obtained by personal communication from the Gothenburg RCT.[25]

The Jiashan trial was the only eligible study that evaluated an immunochemical test and was therefore included for comparative purposes. Nevertheless, differences in age and healthcare environment somewhat limit the clinical relevance of this study. It was difficult to evaluate what influence the young average age of the study population in this RCT may have had on the efficacy of screening to reduce CRC mortality. However, given the overall youth of the study population (and therefore the probable lower incidence of CRC in such a group) the impact of screening would likely have been reduced in this trial.

The investigators justified their choice of start age by explaining that CRC occurs approximately 10 years earlier in Chinese than in Westerners; this ethnic difference also limits how applicable the results of the Jiashan RCT are to the New Zealand population.[16]

Since the management of screen positive participants differs from that of the three studies that examined guaiac FOBTs, the results from this study are not directly

comparable. Although the evidence from this study suggests that a reduction in rectal cancer may be achievable with the use of an immunochemical test, for the reasons outlined above and in the results section this evidence is less robust than that provided by the other three RCTs included in this section.

Although population-based surveillance using flexible sigmoidoscopy has been investigated,[26] no large RCT of this method has been completed that provided incidence and mortality data. Three large ongoing trials are investigating flexible sigmoidoscopy as either one-off or repeated screening for average-risk men and women aged from their mid-50s.

Preliminary results are promising in terms of feasibility and acceptability. However, incidence and mortality data will not be available before 2008 for the two trials investigating one-off screening (*personal correspondence,* Professor Wendy Atkin, principal investigator, Flexible Sigmoidoscopy Screening Trial, 15 February 2005; *personal correspondence,* Dr Carlo Senore, SCORE Trial, 16 March, 2005), and until 2010–2012 for the trial of repeated screening (*personal correspondence,* Dr Schoen, investigator, The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 23 February 2005).

The Funen-2 trial with FOBT followed by FS had a short follow-up period and non-repeat screening and was not designed as a mortality study. The trial evidence does not support a FOBT and FS combined screening strategy in asymptomatic middle-aged populations over screening involving FOBT alone. These results could reflect poor compliance in the combined screening group and, in those attending, few additional positive results from FOBT that were not already reported by FS.

The Norwegian Colorectal Cancer Prevention (NORCCAP) trial[2] comparing FS screening with no intervention considered FOBT and FS combined compared with FS alone within the trial intervention arm. Data on CRC incidence and mortality is expected to become available in late 2007 (*personal correspondence,* Professor G. Hoff, Investigator, NORCCAP Screening Trial, 8 March 2005).

Conclusion

This review has examined the efficacy of screening for CRC using FOBT testing with or without FS. The estimated reduction in CRC mortality resulting from screening with guaiac-based FOBT in large randomised controlled trials with long follow-up provides support for the use of this test. No such evidence exists for screening with FS either alone, or in combination with FOBT, but this should be re-evaluated once data become available from four large ongoing trials.

To replicate the mortality reductions found in the FOBT trials, participation in a screening programme would need to be equivalent or higher. Screening acceptability may represent one of the biggest challenges for FOBT screening. This paper has not examined other issues of relevance to the use of screening for colorectal cancer screening, including risk of harm from screening, resources available for the management of screen positive individuals and the economic implications resulting from screening. These are discussed further in the full report of the systematic review.[5] Such factors are important considerations that may influence the decision to introduce a colorectal screening programme based on FOBT testing.

Competing interests: None.

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