The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer

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Abstract

***Aims*—To determine the harm that ensues from faecal occult blood (FOB) screening for colorectal cancer.**

***Methods*—150 251 people were randomly allocated either to receive biennial Haemoccult FOB tests (n =75 253) or not to be contacted (n=74 998). Study group patients returning positive tests were offered colonic investigation; 1774 underwent complete investigation of the colon.**

***Results*—There was no significant difference in the stage at presentation of interval versus control group cancers. Survival in the interval cancer group was significantly prolonged compared with the control group. Sensitivity for colonoscopy or flexible sigmoidoscopy and double contrast barium enema (DCBE) was 96.7%. There were no complications of DCBE but seven (0.5%) complications of colonoscopy, of which six required surgical intervention. There were no colonoscopy related deaths. No patients without colorectal cancer died within 30 days of colonic investigation. Five patients died within 30 days of surgery for screen detected colorectal neoplasia and a further two died without having surgery. Six patients died after 30 days but within two years of surgery for screen detected benign adenomas or stage A cancers; in all cases the cause of death was not related to colorectal cancer.**

***Conclusions*—There was investigation related morbidity but no mortality and little to support overdiagnosis bias. The group returning falsely negative tests had a better outcome compared with the whole control group. There is a negative side to any screening programme but mortality reduction in this and other trials suggests that a national programme of colorectal cancer screening should be given consideration.**

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Colorectal cancer is the second most common cause of death from malignant disease in England and Wales, resulting in approximately 16 000 deaths in 1993.[1] Although there have been advances in the management of symptomatic colorectal cancer, there has been little overall reduction in mortality over the past three decades. Tumour stage is an important determinant of outcome; 24–27% of patients have metastatic disease at presentation and in only 6–10% is the tumour confined to the bowel wall (Dukes' stage A).[2–4] Diagnosis prior to the development of symptoms may be an important means of reducing the mortality from colorectal cancer.

Five case control studies[5–9] and three randomised controlled trials[10–12] have shown a reduction in the risk of dying of colorectal cancer and a reduction in disease specific mortality by faecal occult blood (FOB) test screening. A recent meta-analysis of the six controlled Haemoccult screening trials found a 16% (95% confidence interval (CI) 7–23%) reduction in colorectal cancer mortality.[13] However, cancer screening programmes have drawbacks including financial costs,[14] and screening induced morbidity (including psychological effects[15]) and mortality.

Screening induced morbidity and mortality is a theme that has been developed by Ahlquist who sought an explanation for the failure to show an overall (rather than disease specific) mortality reduction in the screened groups. He has suggested that deaths prevented by screening have been cancelled out by deaths actually caused by screening. He implicates false negative results because of FOB test sensitivity falsely reassuring patients and leading to delayed cancer diagnosis and poorer outcome; the harm caused by colonic evaluation in the patients with no significant colonic neoplasia (both direct injury and cardiac deaths secondary to the effects of bowel preparation and/or sedation); and "overdiagnosis" bias, where asymptomatic colorectal tumours, which possess an innocuous natural history and would not have harmed their hosts during their remaining lifetime, are detected and treated.[16]

We would argue that the purpose of screening is to reduce disease specific rather than overall mortality. Even if the beneficial effect on reduction in mortality from a single disease can be shown by a randomised trial, it would be unrealistic to expect to show an effect on overall mortality unless the disease caused a very high proportion of all deaths. As colorectal cancer represents 12% of all cancer deaths and

Abbreviations used in this paper: FOB, faecal occult blood; DCBE, double contrast barium enema; FHSA, Family Health Service Authority; NNH, number needed to be harmed; NNT, number needed to treat.

2% of all deaths, a trial to show an effect on all cause mortality would require an astronomical sample size.

Notwithstanding this, and that we have already shown a significant reduction in mortality by screening, we address the three issues raised by Ahlquist by drawing on data from the Nottingham trial of FOB screening.[11]

Firstly, he suggests that false negative results (usually because of low FOB test sensitivity) falsely reassure patients and lead to delayed cancer diagnosis and poorer outcome. This can be tested by comparing the outcome in patients in the interval cancer group with the control group. The interval group comprises those whose cancer presented symptomatically in the interval following a negative FOB test or following a positive test but where further investigation was refused or negative. Those who were not offered screening at all and who developed colorectal cancer comprise the control group. We also consider the sensitivity of the colonic investigation by (harshly) assuming that all colorectal cancers presenting in the interval following a positive FOB test were present at the time of the colonoscopy and were therefore missed by it (irrespective of the interval and stage at presentation).

Secondly, Ahlquist implicates the possible harm caused by colonic evaluation (both direct injury and cardiac deaths secondary to the effects of bowel preparation and/or sedation), particularly in the patients found not to have significant colonic neoplasia. This is addressed by considering the direct and indirect complications, including deaths, of double contrast barium enema (DCBE) and colonoscopy. The indirect harm is gauged by considering patients who died within 30 days of colonoscopy and scrutinising their records to assess the impact of the investigation on their death.

Finally, it is suggested that some of the harm from screening comes through overdiagnosis. This term has been used to describe a number of different concepts in relation to screening. In this article, it refers to those individuals where a cancer is diagnosed by screening which would never have presented itself symptomatically in the remaining lifetime of that patient—that is, where it would have been an incidental finding at postmortem examination. This can be estimated (though the measure used is likely to overstate the impact of this potential bias) by counting the number of patients dying within 30 days of surgery for any screen detected colorectal cancer or adenoma; or those dying after 30 days but within two years of surgery for screen detected benign adenomas or stage A cancers. These individuals might be considered to have been overdiagnosed if the cause of death was considered on death review not to be related to colorectal cancer.

Methods

In the Nottingham area of England, 150 251 people aged 45–74 years were randomly allocated either to receive biennial Haemoccult FOB tests (study group) or not to be contacted (control group). Details of the study method have been reported previously.[11]

Control group subjects were identified but not approached. They received no intervention but their incidence of colorectal cancer and their mortality was monitored. Study group subjects were sent a Haemoccult (SmithKline Diagnostics, San Jose, USA) FOB test kit, together with instructions and an explanatory letter from their general practitioner (GP) which invited them to complete and return the test. Those accepting the test placed two samples from each of three successive stools on Haemoccult test cards which were posted to their general practice premises. The cards were collected each day and taken to the Department of Surgery for testing. This was carried out without prior rehydration.

In the pilot study subjects with one or more test squares showing a positive result were investigated by DCBE and flexible sigmoidoscopy. In the main study, colonoscopy was the primary means of investigation (supplemented by DCBE if incomplete) and dietary restriction was practised prior to stool collection in order to minimise the false positive rate.

Individuals found to have cancer or adenomas were treated and subsequently transferred to endoscopic follow up programmes. Those with negative tests, together with those with positive tests where no neoplasia was found following colonic investigation, were invited to undertake repeat screens at two yearly intervals. Screening was terminated in February 1995 by which time all subjects had the opportunity to be screened at least three times.

The development of cancer in study and control groups has been identified from the histopathology registers of local hospitals, the Trent Regional Cancer Registry, and by reports from the general practitioners. The entire population has been flagged at the National Health Service Central Registry and from there the Office of Population Censuses and Surveys (OPCS) routinely notifies the trial coordinator (CMM) of the date and causes of death of trial participants, and the date and diagnosis of those registered as having cancer, including people no longer living in the Nottingham area. Information on deaths was also obtained locally from Family Health Service Authority (FHSA) and GP records.

Cancers in the study group have been classified as screen detected, interval cancers, and cancers in those never screened. Screen detected cancers are all those diagnosed as a result of investigation following a positive test. Interval cancers are those diagnosed following a negative test, or following a positive test where further investigation was negative, or was refused. All cancers have been staged according to the Turnbull modification[17] of Dukes' staging,[18] in which cases with metastatic disease are classified as stage D.

All deaths in subjects diagnosed with colorectal cancer, and deaths where colorectal cancer or "carcinomatosis, primary unspecified" was noted on the death certificate, have been scrutinised. Colorectal cancer was verified as cause of death where this was felt to be definite or probable, based on well defined clinical, radiological, and/or histological criteria. The

reviewers were blinded to the group (study or control) from which the deceased patient came. Any patient dying within 30 days of surgery for colorectal cancer was said to have died of the disease in the analysis of mortality but, for the purposes of this paper, these deaths have been scrutinised.

Deaths to June 1996 were considered. Comparisons of proportions were made by the χ^2 test. Comparisons of survival were made by the log rank test.

Results

In total 960 (2.1%) people required colonic investigation following their first screen. Following rescreening 1090 (1.2%) tests were positive; 1778 people (4.0% of those accepting screening at least once) underwent examination of their rectum and colon on one or more occasions. In this group 1474 colonoscopies and 738 DCBEs were done.

During the course of the trial, 236 cancers were detected by screening, 249 interval cancers presented, 400 cancers were diagnosed in non-participants, and 856 presented in the control group. A further eight cancers in the study group were diagnosed during endoscopic surveillance of a screen detected lesion.

The interval cancers included 13 following a positive test (two investigated by colonoscopy and six by DCBE where no abnormality was found, and five where further investigation was refused). This suggests a sensitivity for colonic investigation, based on interval cancer rates, of 236/(236+6+2) = 96.7% (95% CI 94.5–99.0%). Of the eight interval cancers following a positive test and negative investigation (stage A=0, B=1, C=3, D=4), none presented in the first year, six in the second year, and one in the third year. The remaining case presented 13 years following a positive test. Colonoscopy missed two cancers—one in the sigmoid colon, the other in the caecum. All six cancers missed by DCBE were located proximal to the hepatic flexure. Of these six, barium enema was the primary means of investigation in four; in the other two, it was carried out following an incomplete colonoscopy.

Table 1 shows the stage distribution of the interval and control group cancers. The interval group (n=249) had a higher (but not significantly) proportion of stage A tumours (16% versus 11%, p=0.05) than and a similar proportion of advanced (stage C, D, and unknown) tumours (54% versus 56%, p>0.1) to the control group (n=856). However, survival was better for the interval cancers (p<0.01); this advantage is reduced but remains significant if the stage distribution is taken into account (p=0.02).

Table 1 Stage distribution of control and interval cancers

	Interval group			
Stage	*Following negative test*	*Following positive test*	*Total*	*Control group*
A	38	1	39 (16%)	95 (11%)
B	74	2	76 (31%)	285 (33%)
C	66	5	71 (29%)	264 (31%)
D	56	5	61 (24%)	179 (21%)
Unknown	2	0	2 (1%)	33 (4%)
Total	236	13	249	856

There were no complications of DCBE but seven (7/1474 = 0.5%) complications of colonoscopy (five perforations, one major bleed, one snare entrapment), of which six required surgical intervention. None of these patients died and there were no colonoscopy related deaths. No patients died within 30 days of colonic investigation who were not being treated for detected colorectal neoplasia.

Five patients died within 30 days (postoperative days 0, 1, 4, 9, 14) of surgery for screen detected colorectal cancer or adenoma (adenoma=1, cancer stages A=0, B=1, C=2, D=1). Cause of death in these cases was myocardial infarction in one, anastomotic leak in one, pulmonary embolus in two, and carcinomatosis in one. Preoperative investigation revealed metastatic disease in two further patients who died within 30 days of diagnosis without having surgery (stage D=2). Thirty six patients died after 30 days but within two years of surgery (26 from recurrent colorectal cancer, four from other malignancy, three from cardiovascular causes, one from chronic obstructive pulmonary disease, and two from degenerative neurological disease). Of this group of 36, two had had screen detected benign adenomas and four had had stage A cancers. The cause of death in all six was considered on death review not to be related to colorectal cancer (three, other malignancy; three, cardiovascular). Clearly, all 43 patients mentioned could not be considered to have benefited by the earlier detection of their colorectal cancer. However, of this group of 43, only the six patients with adenomas or stage A cancers (who died of unrelated other conditions within two years of detection of the tumour by screening) would probably never have presented with their tumour during their remaining lifetime. In other words, only six patients would have probably been "overdiagnosed".

Discussion

This study has previously reported a statistically significant 15% reduction in colorectal cancer mortality by FOB screening but no reduction in all cause mortality.[10] This supports the findings of five case control studies[5–9] and two other randomised controlled trials[10 12]; and is similar to the findings of a meta-analysis of the six controlled trials.[13] The case for a national screening programme is currently being considered by the Department of Health's National Screening Committee. However, opponents of FOB screening point to the financial costs and psychological risks. Both issues have been prospectively addressed in the setting of this trial (M Parker, personal communication),[19] but Ahlquist has raised other areas of concern.[16]

Patients with colorectal cancer who complete a FOB test which is negative may be falsely reassured and delay presentation with symptoms. If this were the case, we should expect a less favourable stage distribution and

worse survival in this group compared with controls; the opposite was, in fact, observed, both in this and in the Danish trial.[12]

It might also be argued that, had the tumours missed by colonic investigation been detected at screening, they could have been treated endoscopically, potentially avoiding the need for surgery. This is unlikely as none of the interval cancers was at stage A while seven of the eight were stage C or D when subsequently presenting with symptoms. This failure of colonoscopy and/or barium enema equates to a sensitivity for investigation of 96.7%, similar to the findings of a recent large US study.[20] It is not possible to quantify the relative sensitivities of colonoscopy versus DCBE in our study. However, as in the study of Rex *et al*,[20] we have found that DCBE was more likely to miss cancers than colonoscopy.

Colonoscopy is potentially hazardous.[21] In this trial, six major complications of colonoscopy (0.5%) occurred but with no mortality. Five of the complications were the result of a therapeutic intervention and one occurred in a diagnostic procedure. The latter was a retroperitoneal perforation in a segment of severe diverticular disease and this patient did not require surgical intervention. This paper addresses only those colonic evaluations carried out as a direct result of a positive FOB test. It should be emphasised that any colorectal cancer screening programme, through the detection of adenomas, will generate a substantial number of follow up surveillance colonoscopies. Although there was no mortality, the morbidity does highlight the need for careful audit of colonoscopy performance, particularly if national screening were to be introduced. This is reinforced by the recent highly publicised failings in the cervical cancer screening programme. A recent review of this programme has highlighted the need to emphasise four areas: (1) the aim of the screening test (cervical screening is not a test for cancer but for abnormal cells that might lead to cancer); (2) the fallibility of the test (it is not 100% accurate); (3) the need for reporting symptoms irrespective of the result of the screening test (abnormal bleeding); and (4) the screening programme is effective (cervical screening prevents up to 3900 deaths per year).[22] A future national colorectal cancer screening programme must address and emphasise these same four issues.

There was no serious morbidity and no mortality in relation to DCBE, acknowledged to be a safer procedure than colonoscopy. As regards cardiorespiratory (or any other) mortality relating to sedation at colonoscopy, no patients (who did not have colorectal cancer) died within 30 days following any colonic investigation. How to investigate individuals with a positive FOB test (colonoscopy versus DCBE and flexible sigmoidoscopy) has been a key question for the National Screening Committee to answer. It is clear that, at present in the United Kingdom, there is insufficient availability of both colonoscopy and DCBE—the introduction of a screening programme will, of necessity, address this. In due course, rapid developments in computed tomographic colography ("virtual colonoscopy")[23] may supplant these diagnostic procedures.

It is possible that certain individuals with screen detected cancers would have died of other disease before their tumour declared itself. These individuals will have suffered "unnecessary" investigation and surgery and needless anxiety. It is difficult to quantify this overdiagnosis but it may be reflected in 30 day mortality for those with screen detected cancers. Five patients died a median of four (range 0–14) days postoperatively, one of whom had had an anastomotic leak. Of those dying after 30 days but within two years, only four had stage A disease, three of whom died of other malignancy. It would seem that the scale of overdiagnosis is small.

We have shown and quantified some of the physical risks of screening in this paper while the financial costs of the study have been previously addressed.[19] A new method of expressing the costs and benefits of a medical intervention has been recently described. This is the number that need to be treated (NNT), and the number that need to be harmed (NNH), to produce a given beneficial outcome. This concept can be adapted to cancer screening[24] to inform the increasingly visible debate on rationing. We have previously reported that 44 838 individuals have accepted at least one offer of screening; and that, at median follow up of 7.8 years, there were 60 fewer deaths attributed to colorectal cancer in the group offered screening compared with controls.[11] This report has highlighted the six individuals who have been sufficiently harmed by the process of investigation to require surgical intervention. Therefore, in this study, the number that needed to be screened (over 7.8 years) to prevent one colorectal cancer death was 747 (44 838/60) (NNT variant). Conversely, one person will be sufficiently harmed by the process of investigation to require surgical intervention for every 10 (60/6) colorectal cancer deaths prevented (NNH variant). The NNT variant for the Danish[12] and Minnesota[10] trials was 470 (20 672/40) over 10 years and 360 (14 034/39) over 13 years respectively.

The type of adverse consequences discussed are common to any cancer screening programme. However, they must be recognised (by both the medical profession and, more importantly, by the population as a whole) as being implicit to a programme whose overall effect is beneficial. They must also be minimised (and be seen to be minimised) by close attention to quality control and audit. Only then will public confidence, essential to the success of any cancer screening programme, be maintained. The importance of this area needs considerable emphasis.

The accumulating evidence is that FOB screening reduces colorectal cancer mortality. Serious consideration should be given to the development of a national colorectal cancer screening programme based on FOB testing.

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