Randomised controlled trial of faecal-occult-blood screening for colorectal cancer

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Summary

Background There is growing evidence that faecal-occult-blood (FOB) screening may reduce colorectal cancer (CRC) mortality, but this reduction in CRC mortality has not been shown in an unselected population-based randomised controlled trial. The aim of this study was to assess the effect of FOB screening on CRC mortality in such a setting.

Methods Between February, 1981, and January, 1991, 152 850 people aged 45–74 years who lived in the Nottingham area of the UK were recruited to our study. Participants were randomly allocated FOB screening (76 466) or no screening (controls; 76 384). Controls were not told about the study and received no intervention. Screening-group participants were sent a Haemoccult FOB test kit with instructions from their family doctor. FOB tests were not rehydrated and dietary restrictions were imposed only for retesting borderline results. Individuals with negative FOB tests at the first screening, together with those who tested positive but in whom no neoplasia was found on colonoscopy, were invited to take part in further screening every 2 years. Screening was stopped in February, 1995, by which time screening-group participants had been offered FOB tests between three and six times. Screening-group participants who had a positive test were offered full colonoscopy. All participants were followed up until June, 1995. The primary outcome measure was CRC mortality.

Findings Of the 152 850 individuals recruited to the study, 2599 could not be traced or had emigrated and were excluded from the analysis. Thus, there were 75 253 participants in the screening group and 74 998 controls. 44 838 (59·6%) screening-group participants completed at least one screening. 28 720 (38·2%) of these individuals completed all the FOB tests they were offered and 16 118 (21·4%) completed at least one screening but not all the tests they were offered. 30 415 (40·4%) did not complete any test. Of 893 cancers (20% stage A) diagnosed in screening-group participants (CRC incidence of 1·49 per 1000 person-years), 236 (26·4%) were detected by FOB screening, 249 (27·9%) presented after a negative FOB test or investigation, and 400 (44·8%) presented in non-responders. The incidence of cancer in the control group (856 cases, 11% stage A) was 1·44 per 1000 person-years. Median follow-up was 7·8 years (range 4·5–14·5). 360 people died from CRC in the screening group compared with 420 in the control group—a 15% reduction in cumulative CRC mortality in the screening group (odds ratio=0·85 [95% CI 0·74–0·98], p=0·026).

Interpretation Our findings together with evidence from other trials suggest that consideration should be given to a national programme of FOB screening to reduce CRC mortality in the general population.

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Introduction

Colorectal cancer (CRC) is the second commonest cause of death from malignant disease in England and Wales, and resulted in about 16 000 deaths in 1993.[1] Although there have been advances in the management of symptomatic CRC, there has been little overall reduction in CRC mortality during the past 30 years. Tumour stage is an important determinant of outcome; 24–28% of patients have metastatic disease at presentation and the tumour is confined to the bowel wall in only 6–10% (Dukes' stage A).[2–4] Early diagnosis before the development of symptoms may be an effective way of reducing CRC mortality.

Tumours diagnosed as a result of screening by faecal-occult-blood (FOB) testing are known to include a higher proportion at a less advanced stage than those presenting symptomatically.[5,6] FOB tests are also cheap,[7] safe, and acceptable to the population.[8] Three case-control studies have shown that FOB screening led to a reduction in the risk of death from CRC,[9–11] but, because of the self-selection bias, these findings must be viewed with caution. The efficacy of screening by FOB tests should be tested by comparison of disease-specific mortality among individuals who are offered screening with unscreened controls in the setting of a randomised controlled trial. Three European randomised controlled trials of population screening for CRC by FOB tests have confirmed that the test has a high rate of compliance and that CRC can be detected at an earlier stage.[6,12,13] The Minnesota study[14] of FOB screening in a volunteer population, reported a significant reduction in disease-specific mortality after annual screening by FOB tests, with a non-significant reduction in the group offered biennial screening. However, in studies of health-conscious volunteers, control-group mortality tends to be lower and compliance higher than in the general population,[15] so their findings may not give a realistic estimate of the effect in an unselected population.

In this randomised controlled trial we assessed the effect of biennial screening by FOB tests on CRC mortality in the general population of the Nottingham area of the UK. We report here the initial CRC mortality data.

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Methods

We recruited individuals for the pilot study between February, 1981, and June, 1983,[16] and for the main study between February, 1985, and January, 1991. Individuals who lived in the Nottingham area of the UK were identified according to the general practice at which they were registered. Family Health Service Authority and general practice registers were used to compile a list of men and women aged 50–74 (45–74 years in the pilot study) in each general practice. Family doctors at each practice were asked to remove from this list any person whom they judged should be excluded from the study because of serious illness, including a diagnosis of CRC within the previous 5 years. Before randomisation the remaining individuals were sorted by household (people who lived at the same address); households were then stratified by size, sex (male only, female only, mixed), and average age of eligible members (in 5-year age-groups). This ensured that all eligible members of the household were allocated to the same group. Households were randomly allocated screening by FOB tests (76 466) or no screening (controls; 76 384).

All study participants were allocated a date of entry to the study—the date when the first invitations for screening were sent to screening-group participants in that particular general practice. Because of the time between the compilation of the lists and the invitation for screening, 1053 people (506 screening group, 547 controls) were aged 75 years or older at entry.

Controls were identified but were not told about the study, received no intervention, and continued to use health-care facilities as usual. This approach was judged to be ethical at the time of study design. The study was approved by Nottinghamshire Local Medical Committee and the BMA Ethics Committee.

Screening-group participants were sent a Haemoccult (Rohm Pharma, Weiterstadt, Germany) FOB test kit, together with instructions and an explanatory letter from their family doctor, which invited them to complete and return the test. Individuals who accepted the test took two samples from each of three consecutive stools and sent the completed FOB test cards to their general practice. A cohort within the screening group was asked to test six consecutive stools at the prevalent screen.[17] The FOB test cards were collected daily from each general practice and were taken to the Department of Surgery, Queen's Medical Centre, Nottingham, for testing. The FOB cards were not rehydrated. Completed tests were processed by one of three investigators (CMM supervised). We sent a reminder letter to all screening-group participants who had not returned their tests after 4–6 weeks.

In the pilot study, screening-group participants with one or more test squares on the FOB card that showed a positive result were investigated by double-contrast barium enema and flexible sigmoidoscopy. In the main study, to keep the false-positive rate to a minimum, a repeat test was sent to individuals with up to four positive squares, with a request to restrict their diet for 2 days before taking two samples from six consecutive stools. Only those individuals with five or more positive squares at the first test or those with one or more positive squares at the retest were offered colonoscopy (supplemented by double-contrast barium enema when full colonoscopy could not be done). Screening-group participants with a negative retest were asked to repeat the test, again with dietary restriction, 3 months after the retest and were offered colonoscopy if they tested positive.[18]

Screening-group participants who were found to have CRC or adenomas on colonoscopy were treated and transferred to endoscopic follow-up programmes. Individuals with negative FOB tests, together with those who had positive tests but in whom no neoplasia was found on colonoscopy, were invited to take part in screening every 2 years. People who did not accept the first invitation for screening were not initially reinvited. In September, 1990, in an effort to improve overall compliance, we reinvited every 2 years those individuals who had not previously responded. We stopped screening in February, 1995, by which time all participants had been offered FOB tests between three and six times.

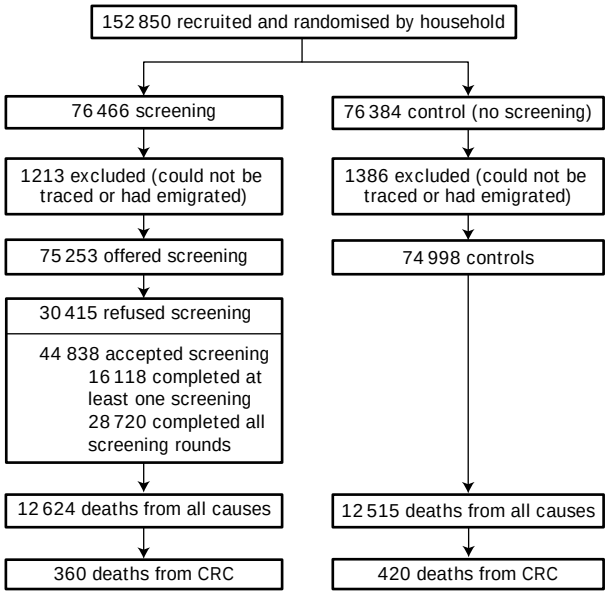

Figure 1: **Trial profile**

We obtained information on the development of CRC in screening-group participants and unscreened controls from the histopathology registers of local hospitals, the Trent Regional Cancer Registry, and from the family doctors' reports. The records of all study participants were flagged on the National Health Service Central Registry database, and the Office of Population Censuses and Surveys routinely notified the study coordinator of the date and causes of death of any study participant, and the date and diagnosis of those who were registered as having cancer, including people who no longer lived in the Nottingham area. Information on deaths was also obtained from the Family Health Service Authority and the records of family doctors. Individuals who could not be traced by the Office of Population Censuses and Surveys or had emigrated were not included in our analysis.

We classifed all cases of CRC in the screening group as: screen-detected (CRC diagnosed on colonoscopy after a positive FOB test); interval (CRC diagnosed after a negative FOB test, or after a positive test where further investigation was negative or was refused); and non-responders (CRC diagnosed in individuals who had not been screened). Individuals who had a diagnosis of CRC confirmed during endoscopic follow-up were a further category. The staging of tumours was done according to the Turnbull modification of Dukes' staging,[19] in which cases with metastatic disease are classified as stage D.[20] Adenomas treated by endoscopic polypectomy and found to contain invasive cancer were classified as stage A. The histology of all cancers treated by polypectomy was reviewed by a single pathologist (PDJ), and 23 cases of CRC with doubtful invasion were reclassified as severely dysplastic adenomas. The assessment of stage of CRC and classification of adenomas was done by pathologists unaware of the participant's study group.

In our analysis the results of the first round of screening were separated according to whether the FOB test was completed on first invitation or only after reinvitation at a later date. Results of rescreening are presented for rescreen within 2 years, 3 months (allowing a possible 3-month delay in invitation), and those, mostly due to refusal by the participant, for which the interval between tests was longer.

After adjustment for deaths from all causes, we calculated the number of person-years in the screening and control groups from date of study entry to June 30, 1995; this date was determined by the MRC Study Monitoring Committee. CRC incidence rates and mortality rates from CRC and from all causes were calculated per 1000 person-years. We excluded all deaths attributable to CRC when the diagnosis of CRC had been made before the date of study entry.

Age (years)	Control		Screening	
	Men (n=36 042)	Women (n=38 956)	Men (n=36 130)	Women (n=39 123)
45–49	1463 (4%)	1318 (3%)	1394 (4%)	1335 (3%)
50–54	7917 (22%)	7910 (20%)	8049 (22%)	7948 (20%)
55–59	8052 (22%)	8070 (21%)	7993 (22%)	8152 (21%)
60–64	7532 (21%)	7899 (20%)	7461 (21%)	8023 (21%)
65–69	6217 (17%)	7241 (19%)	6386 (18%)	7232 (18%)
>70	4861 (13%)	6518 (17%)	4847 (13%)	6433 (16%)

Table 1: **Age and sex distributions at entry to study**

Age (years)	Number (% of age and sex subgroup) who accepted first screening	
	Men	Women
45–49	469 (34%)	575 (43%)
50–54	4067 (51%)	4654 (59%)
55–59	4159 (52%)	4822 (59%)
60–64	4047 (54%)	4620 (58%)
65–69	3447 (54%)	3913 (54%)
>70	2395 (49%)	3046 (47%)
Total (% of total screening group)	18 584 (51%)	21 630 (55%)

Table 2: **Acceptance of first FOB screening by sex and age**

Certification of CRC as a cause of death can be inaccurate,[21] we therefore also carried out structured case-note reviews of certified and registered CRC cases for more reliable information on causes of death. Thus, CRC mortality rates (excluding squamous-cell anal cancer) were calculated from both the underlying cause of death as stated on the death certificate (certified)[22] and the verified cause of death obtained after review of the case-notes. All deaths in participants diagnosed with CRC, and deaths for which CRC or "carcinomatosis, primary unspecified" was noted on the death certificate, were scrutinised. CRC was verified as the cause of death when this cause seemed to be definite or probable, based on well-defined clinical, radiological, and histological criteria. Deaths that occurred in the first 28 days after surgery for CRC were deemed to have been from CRC. When the cause of death was uncertain, the case-notes were reviewed by a second investigator, and when they disagreed about the cause of death the case-notes were reviewed by a third investigator who made the final decision. Investigators were unaware of the screening status of study participants throughout the assessment of CRC mortality.

The primary outcome measure was CRC mortality. The study was originally designed to have 80% power to detect a 23% reduction in mortality at the 5% significance level. The sample size was increased from 106 000 to 156 000 in 1989 in the light of lower than anticipated control-group mortality.[23] Rates of death from CRC in the screening and control groups were compared by a Poisson log-linear model to calculate the CI and to investigate the effect of age and sex. Survival was calculated by the Kaplan-Meier product limit method from the date of diagnosis of CRC censoring at the date of death or at June 30, 1995. Survival in the two groups was compared by the log-rank test. Proportions were compared by the χ^2 test.

Results

The trial profile shows participant numbers throughout the study (figure 1). Of the 152 850 individuals recruited into the study and randomised to screening (76 466) and control groups (76 384), 2599 (1·7%) could not be traced by the Office of Population Censuses and Surveys or had emigrated and were, therefore, excluded from the analysis. Thus, of the remaining 150 251 study participants, 75 253 were in the screening group and 74 998 were unscreened controls. The groups were well matched in terms of age and sex (table 1). The median follow-up was 7·8 years (range 4·5–14·5). Thus, the number of person-years in the two groups is 597 944 and 596 369, respectively.

During the study, individuals in the screening group were offered FOB tests between three and six times according to the date of study entry. 28 720 (38·2%) screening-group participants completed all the FOB tests they were offered, 16 118 (21·4%) completed at least one but not all of the FOB tests they were offered, and 30 415 (40·4%) did not complete any FOB tests. The non-participants included 489 (1·6%), for whom the first letter of invitation was returned by the Post Office as unknown at that address. We decided to include these non-responders in our analysis to ensure comparability with the control group.

In the screening group, acceptance of testing ranged from 29% to 74% according to the general practice screened. Compliance improved from 36·9% during the pilot phase of the study to 57·0% during the main study. Of the 75 253 screening-group participants, 40 214 (53·4%) completed the first screening. Table 2 shows how acceptance of the first test varied by age and sex. The 35 039 individuals who refused the first invitation for screening were reinvited and 4624 (6·1%) accepted. Thus, 44 838 (59·6%) screening-group participants completed at least one screening.

960 (2·1%) people needed full investigation after their first FOB screen. After rescreening, 1090 (1·2%) FOB tests were positive. The predictive values for a positive FOB test for detection of neoplasia and carcinoma are shown in table 3. Detection rates for adenomas and CRC after positive FOB tests were higher in individuals aged 65 years or older at study entry than in the younger participants (7·7 *vs* 4·4 for adenomas, 3·4 *vs* 1·1 for CRC, per 1000 screened), and were higher in men than in

	First screening		Rescreening	
	First invitation	Later invitation to those who refused first	Within 27 months*	After 27 months
Number of people who completed FOB test	40 214	4624	79 323	8835
Positive FOB tests				
Number of individuals	837	123	924	166
% of population tested	2·1	2·7	1·2	1·9
Adenomas				
Number of cases	311	46	304	49
Rate per 1000 individuals screened	7·7	9·9	3·8	5·5
CRC				
Number of cases	83	21	110	22
Rate per 1000 individuals screened	2·1	4·5	1·4	2·5
Predictive value (%) of positive FOB test				
For neoplasia	47·1	54·5	44·8	42·8
For cancer	9·9	17·1	11·9	13·3

*Allowing for a 3-month delay in invitation for screening.

Table 3: **Outcome of screening**

	Screening group							Controls
	First screen		Rescreen	Non-responders*	Interval cancers†	Adenoma follow-up	Total	
	First invitation	Later invitation						
Stages of CRC								
Dukes' A	42 (51%)	6 (29%)	49 (37%)	42 (11%)	39 (16%)	3 (38%)	181 (20%)	95 (11%)
Dukes' B	17 (20%)	7 (33%)	47 (36%)	139 (35%)	76 (31%)	0	286 (32%)	285 (33%)
Dukes' C	20 (24%)	7 (33%)	24 (18%)	89 (22%)	71 (29%)	4 (50%)	215 (24%)	264 (31%)
Dukes' D	4 (5%)	1 (5%)	8 (6%)	117 (29%)	61 (24%)	1 (13%)	192 (22%)	179 (21%)
Not known	0	0	4 (3%)	13 (3%)	2 (1%)	0	19 (2%)	33 (4%)
Total CRC	83	21	132	400	249	8	893	856

*Did not respond to any screening round. †Had negative FOB test at the screening before diagnosis of CRC was made or was not detected by investigation after a positive test.

Table 4: **Stage of CRC in screening and control groups**

women (7·2 *vs* 3·8, 2·3 *vs* 1·5 per 1000 screened). The detection rate for CRC was also higher in participants who refused the first invitation for screening but accepted after reinvitation, possibly because of increasing age or minor symptoms that prompted them to respond. Of the 236 cancers detected by screening, 174 (74%) were in the rectum or sigmoid colon. 1778 screening-group participants (4·0% of those who accepted at least one FOB test) underwent full colonoscopy on one or more occasions.

During the study, 236 cases of CRC were detected by screening, 249 interval cancers presented, 400 were diagnosed in non-responders, and 856 were diagnosed in the control group. A further eight cases of CRC were diagnosed in the screening group during endoscopic follow-up of a screen-detected lesion. Of the 249 interval cancers, 13 were diagnosed after a positive FOB test—two had been investigated by colonoscopy and six by double-contrast barium enema but no abnormality had been found, and five were in individuals who refused further investigation. 236 interval cancers were diagnosed after a negative FOB test: 73 in the first year; 74 in the second year; 27 in the third year; and 62 up to 13 years after a negative FOB test.

The distribution of stages of CRC is shown in table 4. The proportion of stage A tumours was significantly higher in the screening group than in the control group (20 *vs* 11%, $p<0·001$), whereas the proportion of advanced tumours (stage C and D) was significantly lower in the screening group than in the control group (46 *vs* 52%, $p<0·01$). The incidence of advanced CRC (stage C and D) was lower in the screening group than in controls (ratio=0·91 [95% CI 0·80–1·04]); and was lower in people who accepted the first screening invitation than in those who refused the first invitation (ratio=0·76 [0·63–0·93]). Overall, CRC incidence was higher in the screening group than in the control group (1·49 *vs* 1·44 per 1000 person-years; table 5).

The number of patients with adenomas is shown in table 6. 710 participants had screen-detected adenomas retrieved for histological assessment—128 adenomas were less than 10 mm, 375 were 10–19 mm, and 207 were 20 mm or more, of which three (2·3%), 50 (13·3%), and 44 (21·3%), respectively, were severely dysplastic.

Disease-specific survival of individuals with CRC is shown in figure 2. There was a significant survival advantage for individuals in the screening group over those in the control group ($p<0·0001$). Overall, 12 624 (16·8%) screening-group participants and 12 515 (16·7%) controls died. All-cause mortality was similar in the screening and control groups (table 5), but was significantly greater in individuals in the screening group who refused the first test (25·5 per 1000 person-years) than in controls ($p<0·001$).

The case-notes of 1156 individuals were examined to verify whether CRC was the cause of death. In 133 cases (65 in the screening group and 68 in the control group) there was insufficient information to reach a decision about the cause of death. Of these 133 deaths, 108 were certified as "carcinomatosis, primary unspecified", 11 were certified as due to CRC, and 14 were miscellaneous. For a further three individuals, the case-notes could not be located. We did not include these 136 deaths in our data on verified deaths from CRC. Details of differences between certified and verified deaths from CRC between groups will be reported elsewhere.

The number of verified deaths attributable to CRC was lower in the screening group than in controls (360 *vs*

	Number of cases		Rate (per 1000 person-years)		Rate ratio (95% CI)
	Screening	Control	Screening	Control	
CRC	893	856	1·49	1·44	1·04 (0·95–1·14)
Deaths from verified CRC	360	420	0·60	0·70	0·85 (0·74–0·98)
Deaths from certified CRC (underlying cause)	350	398	0·59	0·67	0·88 (0·76–1·01)
Deaths from all causes	12 624	12 515	21·1	21·0	1·01 (0·98–1·03)

Table 5: **CRC incidence and mortality rates and mortality ratios in screening and control groups**

	Screening group						Control group
	First screen		Rescreen	Non-responders	Interval cancers	Total	
	First invitation	Later invitation					
Adenomas							
<10 mm	38 (12%)	8 (17%)	82 (23%)	49 (41%)	76 (45%)	253 (25%)	129 (35%)
10–19 mm	164 (53%)	22 (48%)	189 (54%)	43 (36%)	63 (37%)	481 (48%)	140 (38%)
⩾20 mm	109 (35%)	16 (35%)	82 (23%)	29 (24%)	31 (18%)	267 (27%)	100 (27%)
Total	311	46	353	121	170	1001	370*

*Included one patient in whom size of adenoma was not known.

Table 6: **Patients with adenomas in screening and control groups**

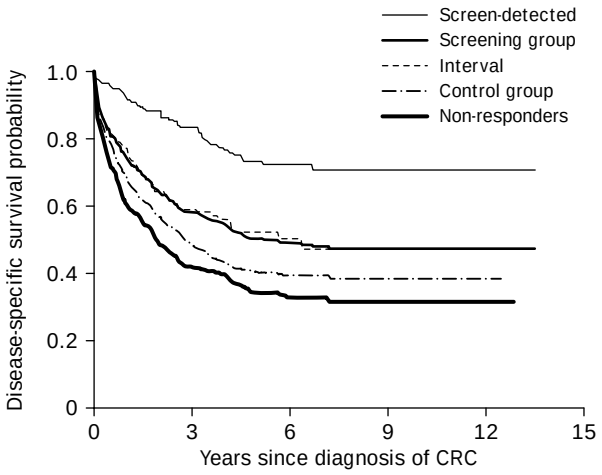

Figure 2: **Disease-specific survival of patients with CRC**

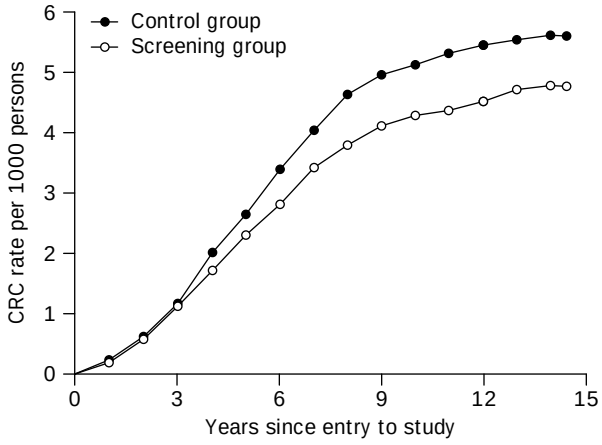

Figure 3: **Cumulative mortality from CRC**

420)—a 15% reduction in verified CRC mortality in the screening group (odds ratio=0·85 [95% CI 0·74–0·98] p=0·026). When the certified, rather than the verified, cause of death was used for the analysis of CRC mortality, the number of deaths from CRC were 350 versus 398 and the estimated mortality reduction was similar though slightly smaller (0·88 [0·76–1·01]). For verified deaths from CRC, the mortality ratio was: 0·87 (0·73–1·05) for men and 0·83 (0·67–1·03) for women; 0·81 (0·66–0·99) for individuals younger than 65 years at study entry and 0·90 (0·74–1·09) for those aged 65 years or older; 0·87 (0·68–1·11) for cancers proximal to the sigmoid colon and and 0·84 (0·70–1·00) for distal cancers.

The reduction in CRC mortality in individuals who accepted the first FOB test compared with the control group was 39% (odds ratio 0·61[0·50–0·74]). There was a relative increase in CRC mortality in people who refused the first FOB test compared with controls (1·13 [0·96–1·33]). Figure 3 shows cumulative CRC mortality in screening and control groups for up to 14 years from study entry; a difference in CRC mortality between the groups emerges after years 3–4. The shape of the curve reflects cumulative recruitment to the study over a 10-year period. Because few people have been in the trial for longer than 10 years, cumulative mortality rates have risen more slowly after this time.

Discussion

It is encouraging that almost 60% of screening-group participants were screened at least once because such compliance was achieved without population education or a statement of definite benefit in the invitation for screening. Compliance would probably improve if a well-organised national screening programme for CRC was introduced in the UK.[24,25]

For CRC screening by FOB test to be effective in the general population, a balance between sensitivity and specificity must be achieved. We were not able to calculate the sensitivity of the FOB tests used in this study because 2 years had not passed since the final round of screening. An earlier analysis, based on more than 50 000 FOB tests, found a sensitivity of 53·6%,[26] which is similar to the 51% sensitivity in Kronborg and colleagues' Danish study.[27] Estimates of sensitivity by the proportional incidence method[28] gave similar results. It is likely that annual screening, rather than biennial, would improve the sensitivity of our FOB screening programme.

Colonoscopy is an expensive procedure that is not without risk.[7,29] For screening by FOB testing to be cost effective, the proportion of false-positive results (commonly caused by red meat or vegetables with a high peroxidase content), should be kept to a minimum by dietary restriction. Robinson et al[26] have shown that retesting of those individuals who had weakly positive FOB tests more than halved the number of people who required colonoscopy during a 4-year period; moreover, the corresponding rate of interval cancers increased by only 3·6%.[26] In the Minnesota study,[14] in which the Hemoccult II test was rehydrated to increase sensitivity, 38% of individuals who were screened annually and 28% of those who were screened biennially underwent colonoscopy at least once, and the positive predictive value of FOB testing for CRC was only 2·2%. In our study, only 4·0% of all individuals who completed FOB tests underwent colonoscopy—the positive predictive value of FOB testing was 12% for CRC and 46% for all neoplasia.

In this study, 4·3% more cancers were detected in the screening group than in the control group. By contrast, in Kronborg and colleagues' Danish trial the number of cases of CRC in the screening and control groups were similar.[30] In the Minnesota study[14] CRC incidence was higher in controls than in the screening group. These conflicting findings may reflect the differing periods of follow-up in the three trials: 8, 10, and 13 years respectively.[14,30]

The survival advantage shown in our screening group compared with the control group should be interpreted with caution, because of the biases inherent in the use of survival as a primary outcome measure in any screening programme. Cumulative reduction in mortality is a more reliable measure of effectiveness than survival. In this study, the 15% reduction in CRC mortality in the screening group is similar to that of the Danish population screening trial.[30]

We believe that our findings (good compliance, a reduction in the rate of advanced CRC, and a significant reduction in CRC mortality in the screening group compared with the control group) support the use of FOB tests in CRC screening programmes. Evidence from other randomised controlled trials of FOB screening also suggest that FOB tests reduce mortality from CRC. We believe that consideration should be given to the establishment of a national screening programme.

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