Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

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Summary

Background Colorectal cancer is the third most common cancer worldwide and has a high mortality rate. We tested the hypothesis that only one flexible sigmoidoscopy screening between 55 and 64 years of age can substantially reduce colorectal cancer incidence and mortality.

Methods This randomised controlled trial was undertaken in 14 UK centres. 170 432 eligible men and women, who had indicated on a previous questionnaire that they would accept an invitation for screening, were randomly allocated to the intervention group (offered flexible sigmoidoscopy screening) or the control group (not contacted). Randomisation by sequential number generation was done centrally in blocks of 12, with stratification by trial centre, general practice, and household type. The primary outcomes were the incidence of colorectal cancer, including prevalent cases detected at screening, and mortality from colorectal cancer. Analyses were intention to treat and per protocol. The trial is registered, number ISRCTN28352761.

Findings 113 195 people were assigned to the control group and 57 237 to the intervention group, of whom 112 939 and 57 099, respectively, were included in the final analyses. 40 674 (71%) people underwent flexible sigmoidoscopy. During screening and median follow-up of 11·2 years (IQR 10·7–11·9), 2524 participants were diagnosed with colorectal cancer (1818 in control group *vs* 706 in intervention group) and 20 543 died (13 768 *vs* 6775; 727 certified from colorectal cancer [538 *vs* 189]). In intention-to-treat analyses, colorectal cancer incidence in the intervention group was reduced by 23% (hazard ratio 0·77, 95% CI 0·70–0·84) and mortality by 31% (0·69, 0·59–0·82). In per-protocol analyses, adjusting for self-selection bias in the intervention group, incidence of colorectal cancer in people attending screening was reduced by 33% (0·67, 0·60–0·76) and mortality by 43% (0·57, 0·45–0·72). Incidence of distal colorectal cancer (rectum and sigmoid colon) was reduced by 50% (0·50, 0·42–0·59; secondary outcome). The numbers needed to be screened to prevent one colorectal cancer diagnosis or death, by the end of the study period, were 191 (95% CI 145–277) and 489 (343–852), respectively.

Interpretation Flexible sigmoidoscopy is a safe and practical test and, when offered only once between ages 55 and 64 years, confers a substantial and longlasting benefit.

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Introduction

Colorectal cancer is the third most frequently diagnosed cancer worldwide, accounting for more than 1 million cases and 600 000 deaths every year.[1] Survival is strongly related to stage at diagnosis, with survival rates of 90% for localised cases.[2] Three randomised controlled trials[3] have shown that biennial screening with the faecal occult blood test, which detects early cases, reduces mortality by around 25% in users of the test, and many countries have introduced screening programmes based on this test.[4]

Screening can potentially prevent colorectal cancers, because most arise from adenomas: predominantly symptomless growths that develop in 20–30% of the population.[5,6] Two-thirds of colorectal cancers and adenomas are located in the rectum and sigmoid colon, which can be examined by flexible sigmoidoscopy. We have shown that flexible sigmoidoscopy is well accepted, safe, and quick,[7–9] and would therefore be a suitable method for population screening if evidence of a worthwhile benefit is shown.

We did a large randomised trial to examine the hypothesis that only one flexible sigmoidoscopy screen undertaken between ages 55 and 64 years is a cost-effective and acceptable method to reduce colorectal cancer incidence and mortality. Our hypothesis is based on observations suggesting that most people who develop a distal colon cancer will have developed an adenoma by 60 years of age,[10] and that removal of adenomas by sigmoidoscopy provides long-term protection against the development of distal colorectal cancer.[11] Results from several epidemiological studies lend support to this hypothesis.[12–14] Baseline findings from the trial were published in 2002,[7] and in this Article we report the results after a median of 11 years of follow-up.

Methods

Study design and participants

The design and rationale for the trial protocol have been described previously.[15] We initially undertook two pilot studies to refine the protocol and to confirm the assumptions on which our sample-size calculations were

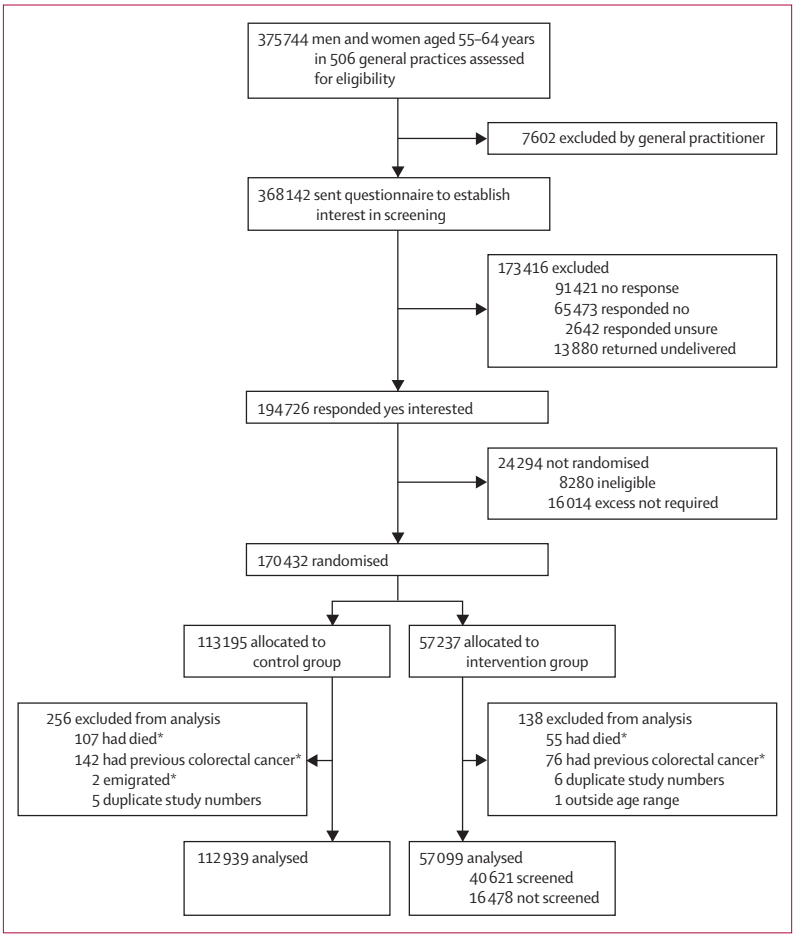

Figure 1: **Trial profile**
*Prerandomisation events.

based.[16] Recruitment and screening started in November, 1994, and were completed in March, 1999. The study took place in 14 UK centres: 11 in England, two in Wales, and one in Scotland. Ethics approval was obtained from local research ethics committees, and all participants undergoing screening provided written informed consent.

All men and women aged between 55 and 64 years and registered with participating general practices were eligible to take part unless they met the following exclusion criteria: inability to provide informed consent; history of colorectal cancer, adenomas, or inflammatory bowel disease; severe or terminal disease; life expectancy less than 5 years; or sigmoidoscopy or colonoscopy within the previous 3 years. Eligible individuals were sent brief information about colorectal cancer and the screening test, together with a short questionnaire including the question: "If you were invited to have the bowel-cancer screening test, would you take up the offer?" Individuals reporting a strong family history of colorectal cancer (two or more close relatives), or symptoms of colorectal cancer were managed outside the trial because randomisation would not have been in their interest.

Randomisation and masking

Eligible individuals, who indicated in the questionnaire that they would take up the offer of screening if invited, were randomly allocated to the intervention (flexible sigmoidoscopy screening) or control groups in the ratio 1:2. Randomisation was stratified by trial centre, general practice within centre, and household type (defined by the number of eligible people in the household who indicated that they would take up the offer of screening: single man, single woman, couples, other). Sequentially numbered randomisation was done centrally in blocks of 12, but with the added constraint of no more than three consecutive allocations to one group within or across blocks. The constraint on blocks contributed to slightly more than a third of individuals being randomly allocated to the intervention group. Participants randomly assigned to screening were offered an appointment; those in the control group were not contacted.

Screening procedure

Flexible sigmoidoscopy screening was done in hospital endoscopy clinics. Details of the screening procedure are described elsewhere.[7] Briefly, participants underwent flexible sigmoidoscopy with polypectomy for small polyps and referral for colonoscopy if they had polyps meeting any of the following high-risk criteria: 1 cm or larger; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease; or 20 or more hyperplastic polyps above the distal rectum. Individuals who had no polyps or only low-risk polyps at flexible sigmoidoscopy were discharged. The occurrence of adverse physical and psychological effects associated with the whole screening procedure, and the quality of the examinations, were carefully monitored and have been reported elsewhere.[7,9,17,18]

Follow-up and endpoints

Since 1999, trial participants have been flagged on the National Health Service Central Register (NHSCR), which provides information about name changes, emigrations, cancer registrations, and dates of death. Information about causes of death as noted in the death certificate was provided by the Office for National Statistics (ONS). UK cancer registries routinely update the NHSCR with cancer registrations, but there can be a time lag. To improve the speed of ascertainment of new cancer diagnoses, we obtained approvals to collect information directly from cancer registries, Hospital Episodes Statistics, and the NHS Bowel Cancer Screening Programme databases. All colorectal cancer diagnoses were confirmed by the registries.

Colorectal cancer sites were defined by the International Classification of Diseases, tenth revision (ICD-10), and included codes C18–C20. Lesions overlapping neighbouring sites (C18.8) were allocated a code for the more distal site, and synchronous lesions

	Control group (n=112 939)			Intervention group (n=57 099)			Hazard ratio (95% CI); intervention *vs* control group	p value
	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)		
Incidence								
All sites	1818*	1 218 334	149 (143–156)	706*†	616 981	114 (106–123)	0·77 (0·70–0·84)	<0·0001
Distal: rectum and sigmoid colon	1192‡	1 220 175	98 (92–103)	386†‡	618 053	62 (57–69)	0·64 (0·57–0·72)	<0·0001
Proximal	628‡	1 222 639	51 (48–56)	311†‡	618 962	50 (45–56)	0·98 (0·85–1·12)	0·75
Mortality								
All-cause	13 768	1 224 523	1124 (1106–1143)	6775	620 045	1093 (1067–1119)	0·97 (0·94–1·00)	0·0519
Colorectal cancer§	538	1 224 523	44 (40–48)	189	620 045	30 (26–35)	0·69 (0·59–0·82)	<0·0001
Non-colorectal cancer causes§	13 230	1 224 523	1080 (1062–1099)	6586	620 045	1062 (1037–1088)	0·98 (0·95–1·01)	0·25
Colorectal cancer (verified¶)	637	1 224 523	52 (48–56)	221	620 045	36 (31–41)	0·68 (0·59–0·80)	<0·0001
Non-colorectal cancer causes (verified¶)	13 131	1 224 523	1072 (1054–1091)	6554	620 045	1057 (1032–1083)	0·99 (0·96–1·02)	0·33

*41 cancers with site not specified were included, 29 in control group and 12 in the intervention group. Only the earliest cancer was counted for patients with more than one cancer. †140 patients had cancers detected at baseline screening (126 distal cancers and 14 proximal cancers). ‡34 patients had both a distal and a proximal cancer (19 synchronous and 15 metachronous): 31 patients in control group and three in the intervention group. §Deaths certified by the Office for National Statistics as colorectal cancer as underlying cause of death by automatic coding. ¶Assignment of colorectal cancer as underlying cause of death by independent expert coder.

Table 1: **Colorectal cancer incidence and mortality in control and intervention groups**

were recorded as separate instances of cancer. Distal cancer was defined as C18.7, C19, and C20 (sigmoid colon and rectum), proximal cancer as C18.0–C18.6 (all sites in the colon proximal to the sigmoid), and site unspecified cancer as C18 and C18.9.

Morphology of colorectal neoplasia was coded with ICD-O2 codes. We included all codes relating to invasive adenocarcinomas (81403, 82103, 82203, 82603, 82613, 82633, 84803, 84813, 84903), and carcinoma not otherwise specified (80103) for cancers in eligible sites that were diagnosed on clinical grounds only.

All deaths certified by the ONS as having colorectal cancer as an underlying cause were included as an endpoint in the analysis of cause-specific mortality. A second analysis was done after blinded verification of assignment of colorectal cancer as an underlying cause of death according to the rules described in the webappendix. Death certificates were supplemented by clinical information when available and scrutinised by an expert and independent coder, who was masked to the trial allocation.

Statistical analysis

The sample size was calculated to give 90% power to detect a 20% difference between the intervention and control groups in incidence of colorectal cancer at 10 years and mortality at 15 years since randomisation, assuming a conservative attendance rate for screening of 55%.[15] Because of the higher than expected attendance rates, revised estimates suggested that the required number of endpoints to show a significant difference in mortality would be achieved at 11 years.[19]

The primary outcomes in this analysis were colorectal cancer incidence and mortality. Secondary outcomes were incidence of distal and proximal cancer, all-cause mortality, and mortality due to non-colorectal cancer causes.

The cutoff for follow-up for this analysis was Dec 31, 2008, although cancer registration was not expected to be complete for the final year. All time-to-event data were censored at emigration, end of follow-up, or death. Only one colorectal cancer per patient was counted in the estimation of incidence of each cancer outcome. In estimation of the incidence of colorectal cancer of all sites, the earliest diagnosis in each patient was used. For the estimation of site-specific (distal or proximal) cancer rates, we used the earliest cancer in that site category.

Results are presented as average incidence rates per 100 000 person-years. Intention-to-treat and per-protocol analyses were undertaken. One minus the Kaplan-Meier estimator of the survival function was used to illustrate time to colorectal cancer and death. The proportionality assumption was violated for incidence of distal and all colorectal cancers. However, the hazards were proportional for most of follow-up, from about 3 years onwards; therefore we used univariate Cox proportional hazards models to estimate hazard ratios and 95% CIs for the intention-to-treat analyses. The Schoenfeld test did not identify any violations of the assumption of proportionality for outcomes other than incidence of distal and all colorectal cancers. Hazard ratios by sex and age group (55–59 and 60–64 years) were illustrated by Forest plots, and significant differences were tested for by the addition of appropriate interaction terms to the models. In the per-protocol analyses, Cuzick and colleagues'[20] method was used to estimate hazard ratios and CIs adjusted for non-compliance. The numbers needed to screen to prevent one colorectal cancer or one death due to colorectal cancer, with 95% CIs, were calculated with Tabar and colleagues' method.[21]

The trial is registered, number ISRCTN28352761.

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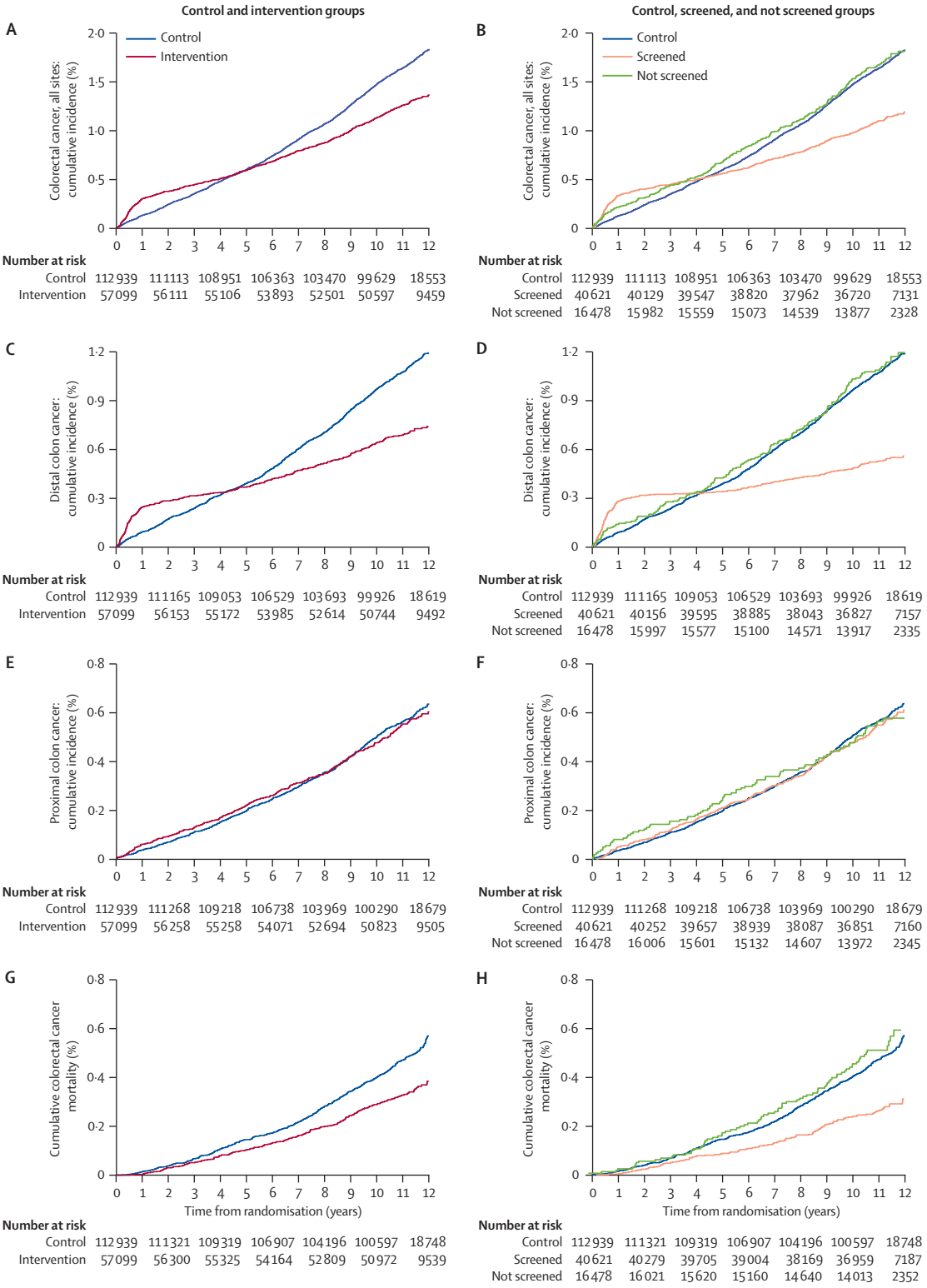

***Figure 2*: Kaplan-Meier estimates of cumulative incidence and mortality**
Colorectal cancer incidence (A and B), distal cancer incidence (C and D), proximal cancer incidence (E and F), and colorectal cancer mortality (G and H). A, C, E, and G are intention-to-treat analyses. B, D, F, and H are per-protocol analyses.

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	Control group (n=112 939)			Intervention group (n=57 099)						Hazard ratio (95% CI); screened *vs* control group*
				Not screened (n=16 478)			Screened (n=40 621)			
	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)	Cases	Person-years	Rate (per 100 000 person-years; 95% CI)	
Incidence										
All sites	1818†	1 218 334	149 (143–156)	261†	172 260	152 (134–171)	445†‡	444 721	100 (91–110)	0·67 (0·60–0·76)
Distal: rectum and sigmoid colon	1192§	1 220 175	98 (92–103)	171§	172 565	99 (85–115)	215‡§	445 488	48 (42–55)	0·50 (0·42–0·59)
Proximal	628§	1 222 639	51 (48–56)	87§	172 879	50 (41–62)	224‡§	446 084	50 (44–57)	0·97 (0·80–1·17)
Mortality										
All-cause	13 768	1 224 523	1124 (1106–1143)	2713	173 191	1566 (1509–1627)	4062	446 854	909 (881–937)	0·95 (0·91–1·00)
Colorectal cancer¶	538	1 224 523	44 (40–48)	78	173 191	45 (36–56)	111	446 854	25 (21–30)	0·57 (0·45–0·72)
Non-colorectal cancer causes¶	13 230	1 224 523	1080 (1062–1099)	2635	173 191	1521 (1461–1581)	3951	446 854	884 (857–912)	0·97 (0·93–1·02)
Colorectal cancer (verified‖)	637	1 224 523	52 (48–56)	94	173 191	54 (44–66)	127	446 854	28 (24–34)	0·56 (0·45–0·69)
Non-colorectal cancer causes (verified‖)	13 131	1 224 523	1072 (1054–1091)	2619	173 191	1512 (1455–1571)	3935	446 854	881 (854–909)	0·98 (0·93–1·03)

*Adjusted for non-compliance with screening. †41 cancers with site not specified were included, 29 in control group and 12 in the intervention group (four not screened and eight screened). Only the earliest cancer was counted for patients with more than one cancer. ‡140 patients had cancers detected at baseline screening (126 distal cancers and 14 proximal cancers). §34 patients had both a distal and a proximal cancer (19 synchronous and 15 metachronous): 31 patients in the control and three in the intervention group (one not screened and two screened). ¶Deaths certified by the Office for National Statistics as colorectal cancer as underlying cause of death by automatic coding. ‖Assignment of colorectal cancer as underlying cause of death by independent expert coder.

Table 2: **Colorectal cancer incidence and mortality by randomisation and compliance with screening**

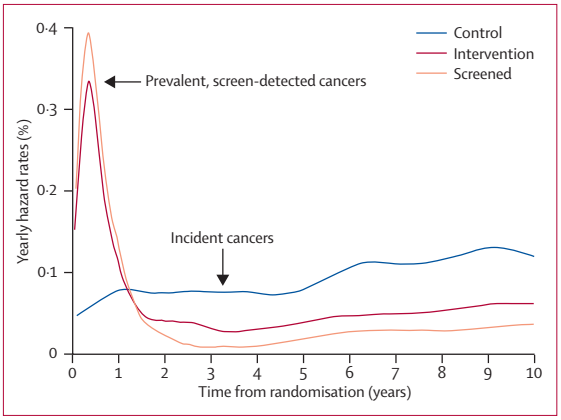

Figure 3: **Smoothed yearly hazard rates for distal cancer (rectum and sigmoid colon)**
Curves are truncated at 10 years of follow-up because of incomplete ascertainment of cancers in the final calendar year of the study.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. KW, IKH, RE, and SD had full access to the data, and WA had final responsibility for submission.

Results

Figure 1 shows the trial profile. 506 (88%) general practices, with 2102 general practitioners, agreed to participate in this study. Local health authorities identified 375 744 patients of the practices, who were aged between 55 and 64 years at the time of the request for data, and general practitioners identified 7602 of them as being ineligible. Questionnaires to assess interest in screening were sent by mail to 368 142 people (50% women), of whom 194 726 (53%) responded that they would take up the offer of screening if invited. Of these, 24 294 people were excluded (figure 1), and 170 432 were randomly assigned: 113 195 to the control group and 57 237 to the intervention group.

40 674 (71%) people attended their screening appointment. After screening, 38 525 (95%) were discharged because either no polyps or only low-risk polyps were detected. 2131 (5%) people were referred for colonoscopy because high-risk polyps were detected, of whom 2051 underwent the procedure and 1745 entered a surveillance programme.

When the cohort was matched with NHSCR data, 162 people (107 control group and 55 intervention group) were found to have died on or before the date of randomisation, 218 people (142 control group and 76 intervention group) had colorectal cancer diagnosed before randomisation, and two (both controls) had emigrated. One individual, who was assigned to the intervention group and attended, had an incorrect birth date (aged 42 years at randomisation). These people were excluded. 11 individuals were randomised twice (mainly because they changed general practitioner; five control group and six intervention group) and the second randomisation was invalidated.

The final analysis cohort consisted of 170 038 participants: 112 939 people were assigned to the control group and 57 099 to the intervention group (of whom 40 621 [71%] attended for screening). There were 29 105 (51%) women in the intervention group and 57 602 (51%) in the control group, and the mean age was 60 years (SD 2·9) in both groups.

	Control group (n=112 939)		Intervention group				Number of events expected in intervention group	Number of events prevented in intervention group	Number needed to screen to prevent one event (95% CI)
			Total (n=57 099)		Screened (n=40 621)				
	n	Rate (per 1000; 95% CI)	n	Rate (per 1000; 95% CI)	n	Rate (per 1000; 95% CI)			
Colorectal cancer diagnosis	1818	16·1 (15·4–16·9)	706	12·4 (11·5–13·3)	445	11·0 (10·0–12·0)	919	213	191 (145–277)
Colorectal cancer death*	538	4·8 (4·4–5·2)	189	3·3 (2·9–3·8)	111	2·7 (2·3–3·3)	272	83	489 (343–852)
Colorectal cancer death (verified†)	637	5·6 (5·2–6·1)	221	3·9 (3·4–4·4)	127	3·1 (2·6–3·7)	322	101	402 (291–647)

*Deaths certified by the Office for National Statistics as colorectal cancer as underlying cause of death by automatic coding. †Assignment of colorectal cancer as underlying cause of death by independent expert coder.

Table 3: **Cumulative incidence of and mortality from colorectal cancer, and the number needed to screen to prevent one event in the present follow-up period**

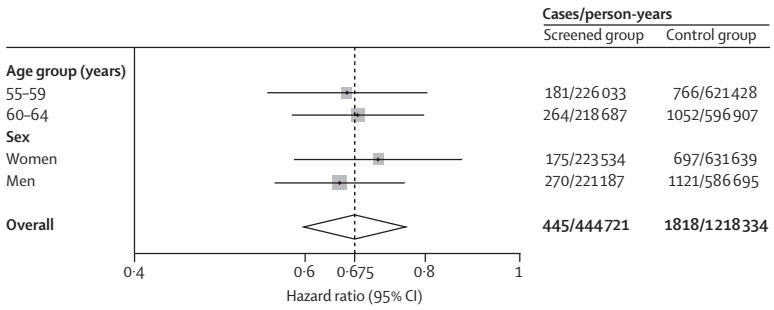

Figure 4: **Hazard ratios for colorectal cancer (all sites) in screened versus control groups by age group and sex**
Hazard ratios are adjusted for non-compliance with screening.

The NHSCR was unable to trace six people in the control group and six in the intervention group, two of whom were screened. A further 234 (<1%) in the intervention group and 451 (<1%) in the control group emigrated. The median follow-up time to death, emigration, loss to follow-up, or Dec 31, 2008, was 11·2 years (IQR 10·7–11·9).

In the analysed cohort, 2674 colorectal cancers were reported of which 2588 (97%) were histologically confirmed, 68 (3%) were diagnosed clinically, and 18 (1%) were ascertained via the death certificate only. We excluded 26 carcinoid tumours, 19 in-situ lesions, five squamous cell carcinomas, two small cell carcinomas, two gastrointestinal stromal tumours, one baso-squamous carcinoma, one leiomyosarcoma, and one nodal marginal zone lymphoma.

2617 colorectal cancers were included in the analyses. These were diagnosed in 2524 participants: 1818 in the control group and 706 in the intervention group. 2438 participants had one colorectal cancer diagnosed and 86 people had two or more (34 had both distal and proximal cancers). Distal cancers were diagnosed in 1192 people in the control group and in 386 in the intervention group (126 detected at screening). Proximal cancers were diagnosed in 628 people in the control group and in 311 people in the intervention group (14 detected at screening).

In an intention-to-treat analysis, the incidence of colorectal cancers (all sites) was significantly lower in the intervention than in the control group (table 1, figure 2A). The incidence of distal colon cancer was reduced by 36%, and proximal incidence by 2% (table 1; figure 2C and 2E).

When the groups were examined according to attendance for screening (per-protocol analysis), the incidence of colorectal cancer in non-attenders was very similar to that in the control group (table 2, figure 2B). The incidence, adjusted for non-compliance, in those who were screened compared with controls was reduced by 33% for all colorectal cancer sites, by 50% for the distal colon, and by 3% for the proximal colon (table 2; figure 2B, 2D, and 2F).

Cumulative incidence for all colorectal and distal cancers, in per-protocol analysis, was higher in the intervention group than the control group for about the first 4 years because of early detection of prevalent cancers at screening (figure 2B and 2D). After this point, the curves began to diverge and the cumulative incidence rates became higher in the control group. The smoothed yearly hazard rates for distal cancers (figure 3) showed a peak in year 1 because of the inclusion of prevalent cancers in the screened group, and after this point incidence was low compared with the control group. We recorded no apparent differences between the intervention and control groups in the curves for cumulative incidence of proximal cancer at any follow-up time (figure 2E and 2F).

We estimated the number of people who needed to be screened to prevent one colorectal cancer diagnosis over the study period to be 191 (95% CI 145–277; table 3).

There were 20 543 deaths in the trial cohort (13 768 in control group, 6775 in the intervention group) of which 727 had colorectal cancer as an underlying cause (538 control group, 189 intervention group) according to death certification by the ONS. Cumulative all-cause mortality at the end of the follow-up period was 11·24 (95% CI 11·06–11·43) deaths per 1000 person-years in the control group and 10·93 (10·67–11·19) per 1000 person-years in the intervention group (table 1). Mortality from colorectal cancer as certified by the ONS was reduced by 31% in the intervention group in the intention-to-treat analysis (table 1, figure 2G). In an adjusted per-protocol analysis, we recorded a 43% reduction in death due to colorectal cancer in people

who attended screening compared with controls (table 2, figure 2H). Screening had no significant effect on mortality due to non-colorectal cancer causes in either the intention-to-treat or per-protocol analyses (table 1, table 2).

We estimated the number of people who needed to be screened to prevent one death due to colorectal cancer to be 489 (95% CI 343–852; table 3).

Independent verification of death certificates identified a further 132 deaths that were probably attributable to colorectal cancer and one that probably should not have been attributed to colorectal cancer. Adjustment for these deaths in our analyses had almost no effect on hazard ratios for rates of colorectal cancer mortality or non-colorectal cancer mortality (table 1, table 2), but substantially reduced the number needed to screen to prevent one death (table 3).

We recorded no significant differences between men and women or between different age groups in the effect of screening on any outcome, in intention-to-treat or per-protocol analyses (figure 4; data shown for incidence of colorectal cancer at all sites).

Discussion

Findings from this large randomised trial have shown that both incidence of and mortality from colorectal cancer are significantly reduced in people undergoing a single flexible sigmoidoscopy examination between 55 and 64 years of age.

After 11 years of follow-up, colorectal cancer incidence was reduced by a third and colorectal cancer mortality by more than 40% in those who underwent screening. Confining results to the rectum and sigmoid colon, incidence was reduced by half in those who were screened. Of the 215 distal cancers diagnosed in this group during 11 years of follow-up, 126 (59%) were detected at screening.[7] Incidence of distal cancers in the postscreening period was very low, and so far there seems to be little attenuation of the protective effect of the screening test (figure 2D, figure 3).

Two other trials of flexible sigmoidoscopy screening will be reported soon. The Italian trial, SCORE,[22] is based on the UK trial protocol and is examining the effect of one screen undertaken between 55 and 64 years of age, with polypectomy of small lesions (<10 mm) done at screening. The US trial, PLCO,[23] is examining the effect of screening every 3–5 years during 55–74 years of age. In this trial, people with abnormalities detected at screening are referred to their personal physician for diagnostic work-up. The Norwegian trial, NORCCAP,[24] which is also examining the effect of once-only sigmoidoscopy at ages 55–64 years, reported results after 7 years of follow-up, at which time no reduction in colorectal cancer incidence was detected.

All colorectal cancer diagnoses received from cancer registries were verified with clinical and pathology records from the hospitals. Colorectal cancer deaths were defined by the ONS, but additionally, underlying causes of death in people with a previous diagnosis of colorectal cancer were reclassified according to rules described in the webappendix. An independent expert coder, who was masked to the trial allocation, recoded the underlying cause of death, relying on information provided on the death certificate supplemented with clinical information when available. Full access to medical records, as in previous studies,[25,26] was not possible. This approach, we believe, is justifiable because Ederer and colleagues[25] showed that different death verification methods yielded largely similar numbers of endpoints in the Minnesota faecal occult blood screening trial. In our study we recorded 727 deaths attributed to colorectal cancer according to the ONS. The independent reviewer identified a further 131 that could probably be attributed to colorectal cancer, suggesting an underestimation of colorectal cancer deaths of 15·3% in this series. However, use of the reviewer's classification of deaths did not change significantly the effect of the intervention on colorectal cancer mortality.

The relative effects of screening on colorectal cancer incidence and mortality were estimated with standard intention-to-treat analyses, which compare outcomes in the control group with the entire group invited for screening irrespective of attendance. Non-attendance, which was 29% in this trial, dilutes the observed effect of screening. Cuzick and colleagues'[20] method can be used to estimate relative risk in attenders compared with the control group, adjusted for the rate of disease in non-attenders. Unusually, colorectal cancer incidence and mortality rates in this trial were very similar in non-attenders and controls (table 2), suggesting that the underlying rates in attenders were also very similar. Nevertheless, we adjusted for non-compliance since the method generates more realistic CIs.

A national bowel cancer screening programme (NBCSP) based on faecal occult blood testing was introduced in a staged manner across England from July, 2006, and some of the participants in our trial took part in this national programme. We matched our dataset with the NBCSP database and noted that 59 of the colorectal cancers had been diagnosed within the screening programme (45 control group and 14 intervention group). We did a sensitivity analysis excluding these cancers on the assumption that they might not have been diagnosed in the absence of screening. The results were almost unchanged (data not shown).

Results of previous case-control studies suggested that flexible sigmoidoscopy could reduce distal colon cancer incidence and mortality by around 70%.[12–14] So far the cumulative reduction in people attending screening in our study is 50%. This lower value is most likely attributable to dominance of screen-detected prevalent cancers in the first 4 years of follow-up (figure 2D), and only after this point did a benefit in terms of incidence

reduction become apparent. If incidence in the screened participants remains low during further follow-up, the magnitude of reduction in cumulative incidence will continue to increase. The cohort will need to be followed up to examine the important issue of the long-term effects of one screening examination.

We recorded no effect of screening on the incidence of cancers in the proximal colon. This result might be expected since flexible sigmoidoscopy does not examine the proximal colon. Several studies[11,27,28] have shown that the risk of cancer beyond the reach of the sigmoidoscope can be predicted from the characteristics of adenomas detected in the rectum and sigmoid colon, and this finding was the basis for selection for baseline colonoscopy and entry into a colonoscopic surveillance programme in this trial. Screened participants who had high-risk polyps were referred for colonoscopy, whereas participants who had no polyps or only low-risk polyps were discharged and their proximal colon was never examined. As a result, colonoscopy was undertaken in 5% of individuals attending screening. In the PLCO and NORCCAP trials,[23,24] criteria for colonoscopy after flexible sigmoidoscopy screening were based on detection of any adenoma or any abnormality, respectively, and consequently colonoscopy rates were three to four times higher than in our study. Whether a significant reduction in incidence of proximal colon cancer is recorded with these protocols will be of interest.

Rates of all-cause mortality excluding colorectal cancer were slightly, although not significantly, reduced in the intervention group compared with the control group. This reassuring finding suggests that the screening did not have unexpected harms.

Economic analyses[29,30] suggest that, with pre-existing assumptions, a once-only flexible sigmoidoscopy screen at age 55 or 60 years would be cost saving, largely because of the avoided costs of treatment resulting from the reduction in incidence. These economic analyses now need to be repeated with the inclusion of our trial data. Factors that will affect the estimated costs of flexible sigmoidoscopy screening are the present and projected costs of treating colorectal cancer[31] and the method of delivery of the screening procedure. Adequately trained nurse practitioners can undertake flexible sigmoidoscopy as competently as can gastroenterologists,[32,33] and public acceptance of nurse-led flexible sigmoidoscopy screening is high.[34,35] If flexible sigmoidoscopy screening were introduced into a national cancer screening programme, both medical and non-medical endoscopy practitioners participating in the programme should meet quality standards and undertake a minimum number of procedures to allow precise measurement of key parameters in a quality assurance programme, as is required for the English NBCSP based on FOBT.[36,37]

A limitation of the trial is that rather than inviting the whole population aged 55–64 years for screening, the trial used a two-stage recruitment procedure whereby eligible individuals were randomly assigned only if they responded to a questionnaire and indicated that they would be likely to attend screening. This procedure increased the power of the study to examine the efficacy of flexible sigmoidoscopy. However, it meant that the compliance rate in the trial was higher than would be expected in a population-based programme, at least in its early years. We are not able to establish whether the observed effect of screening is generalisable to non-participants (those who did not indicate interest on the initial questionnaire). Had we invited the whole population directly, these individuals would probably not have taken up the offer of screening and we would have gained no more information about efficacy in this group. Colorectal cancer incidence in our control group was 149 per 1000 person-years, which is almost exactly as expected from the general population incidence[38] in a group aged 55–64 years followed up for just over 10 years (data not shown). Thus our study population is representative in terms of risk of colorectal cancer, and there is no reason to believe that the potential benefits of screening would differ in people who chose not to participate.

The results from our trial show that flexible sigmoidoscopy is a safe and practical test and, when offered only once to people between ages 55 and 64 years, confers a substantial and longlasting protection from colorectal cancer.

Contributors

WSA, JC, ARH, JW, RE, and JMAN designed the study. WSA, RE, IK-H, and ARH were responsible for trial organisation and data collection. KW did the statistical analysis, under supervision of WSA, SWD, and JC. WSA, IKH, KW, and JW wrote the paper and all authors edited it. DMP was responsible for verification of colorectal cancer as underlying cause of death.

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Conflicts of interest
We declare that we have no conflicts of interest.

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