Articles

Randomised study of screening for colorectal cancer with faecal-occult-blood test

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Summary

Background Case-control studies and a voluntary-based follow-up study have suggested that repeated screening with faecal-occult-blood (FOB) tests can lead to a reduction in mortality from colorectal cancer (CRC). The aim of this randomised study was to compare mortality rates after FOB tests every 2 years during a 10-year period with those of unscreened similar controls.

Methods 140 000 people aged 45–75 years lived in Funen, Denmark, in August, 1985, and were considered for inclusion in our study. Before randomisation we excluded individuals who had CRC or precursor adenomas and those who had taken part in a previous pilot study. Randomisation of 137 485 people in blocks of 14 allocated three per 14 to the screening group (30 967), three per 14 to the control group (30 966), and eight not to be enrolled in the study (75 552). Controls were not told about the study and continued to use health-care facilities as normal. Hemoccult-II blood tests (with dietary restrictions but without rehydration) were sent to screening-group participants. Only those participants who completed the first screening round were invited for further screening—five rounds of screening during a 10-year period. Participants with positive tests were asked to attend a full examination and were offered colonoscopy whenever possible. The primary endpoint was death from CRC.

Findings Of the 30 967 screening-group participants, 20 672 (67%) completed the first screening round and were invited for further screening; more than 90% accepted repeated screenings. During the 10-year study, 481 people in the screening group had a diagnosis of CRC, compared with 483 unscreened controls. There were 205 deaths attributable to CRC in the screening group, compared with 249 deaths in controls. CRC mortality, including deaths attributable to complications from CRC treatment, was significantly lower in the screening group than in controls (mortality ratio 0·82 [95% CI 0·68–0·99]) p=0·03).

Interpretation Our findings indicate that biennial screening by FOB tests can reduce CRC mortality. This study is being continued to improve its statistical power and to assess the effect of the removal of more precursor adenomas in the screening-group participants than in controls on CRC incidence.

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Introduction

Denmark has high incidence and mortality rates for colorectal cancer (CRC)—the incidence of colonic cancer is currently increasing and mortality remains constant, whereas incidence and mortality of rectal cancer are declining. Early stages of CRC are commonly found in only 10–15% of patients with symptoms. However, there is evidence that earlier diagnosis and treatment of CRC in symptom-free patients may reduce mortality. Two case-control studies of screening with faecal-occult-blood (FOB) tests reported reductions in CRC mortality rates of 31%[1] and 57%[2] (the latter reduction was found only in women). Similarly, Winawer and colleagues' non-randomised study[3] showed that annual rigid sigmoidoscopy and FOB tests, rather than sigmoidoscopy alone, led to a reduction in mortality. Mandel and colleagues' voluntary-based randomised study in Minnesota[4] (ie, all participants were informed about randomisation), reported a 33% reduction in CRC mortality rates after 13 years in patients who were offered annual screening for FOB, but a non-significant reduction of 6% in those who were offered biennial screening. Four randomised population trials of screening with FOB tests are under way in Europe,[5–8] but no mortality figures have until now been reported. The main aim of this study was to compare deaths from CRC after biennial screening by FOB tests with deaths from CRC in a similar unscreened population (controls) during a 10-year period.

Methods

This study followed a pilot study of compliance in screening for CRC in which of 685 people, 460 (67%) accepted the Hemoccult-II test.[9] We intended to use three screening rounds with FOB tests during a 5-year period, followed by 5 years of follow-up based on passive case detection. However, after 5 years, the compliance was good and we decided to continue biennial screening for a further 5 years; thus, the study period was from August, 1985, to August, 1995.

Based on the assumption of a CRC mortality rate of 0·9 per 1000 person-years and an annual withdrawal rate of at least 1% from death and other causes,[10] we estimated that about 30 000 controls and 30 000 people in the screening group were required to give a power of 0·70 and a significance level of 0·05 in detecting a 25% reduction in CRC mortality.

Age (years)	Screening		Control	
	Men (n=14 864)	Women (n=16 103)	Men (n=14 850)	Women (n=16 116)
45–49	2566 (17%)	2547 (16%)	2590 (17%)	2515 (16%)
50–54	2720 (18%)	2701 (17%)	2711 (18%)	2770 (17%)
55–59	2618 (18%)	2762 (17%)	2571 (17%)	2688 (17%)
60–64	2538 (17%)	2849 (18%)	2502 (17%)	2877 (18%)
65–69	2284 (15%)	2593 (16%)	2311 (16%)	2589 (16%)
70–74	1918 (13%)	2367 (15%)	1926 (13%)	2395 (15%)
75	220 (2%)	284 (2%)	239 (2%)	282 (2%)

Table 1: **Age and sex of participants at initial screening**

In 1985, 140 000 people aged 45–75 years were living in Funen. Before randomisation we excluded individuals with known CRC, precursors of CRC (adenomas), and distant spread from all types of malignant disorders; these individuals were identified by linkage with hospital inpatient files, the county authorities, and the Civil registration System. People who had taken part in the pilot study were also excluded.

We used a central randomisation procedure based on the population register of the county. The 137 485 inhabitants of Funen were listed according to social security number, but married women were placed after their husbands. Balanced randomisation was done in groups of 14 (three to screening, three to the control group, and eight not enrolled). The computerised randomisation programme was adjusted for married couples, who were always allocated to the same group.

30 967 people were assigned biennial screening and 30 966 were assigned no screening (controls). The primary end part was death attributable to CRC.

Controls were not told about the study and continued to use health-care facilities as usual. This approach was judged to be ethical, and was necessary to obtain an accurate evaluation of general population screening; if the controls had been aware of the aims and interventions used in the study, their behaviour might not have been representative of the general population.

Throughout the 10-year study, we obtained information on all newly diagnosed cases of CRC and precursor adenomas and death certificates for all participants (controls and screening) from the Funen patient database and the county public-health officer. Detailed information on all cases of CRC and adenomas is stored in a central database. In addition, we referred to the Danish National Registry of Patients three times during the study (the last time was in November, 1995). We also cross-checked with the Danish Cancer Society in late 1995 to confirm that no cases of CRC had been missed. Information from death certificates was stored in the database system.

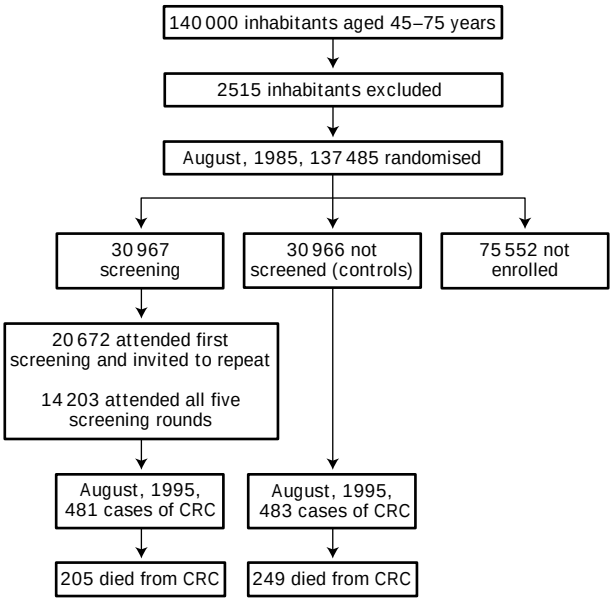

Figure 1: **Study profile**

Screening round	Number of people invited for screening	Number of people screened
1	30 762	20 672 (67%)
2	20 113	18 781 (93%)
3	18 236	17 279 (94%)
4	16 746	15 845 (94%)
5	15 279	14 203 (92%)

Table 2: **Compliance during repeated screening**

Death was certified as due to CRC in patients who had a previous diagnosis of CRC, or had CRC at the time of their death when one of the following criteria was met: histiologically or clinically confirmed distant spread; carcinomatosis or invasion of neighbouring organs; CRC judged to be unresectable; or CRC with perforation causing peritonitis. We were unaware of the participants' screening status during the assessment of death certificates. When we were unable to decide whether CRC was the cause of death, we referred the case to an independent review committee (pathologist, surgeon, specialist in internal medicine, oncologist, general practitioner).[11] Death from complications attributable to CRC was included in the analysis of CRC mortality. Dukes' staging of tumours and classification of adenomas were done by one investigator (CF) under masked conditions.[12]

The Hemoccult-II test has been previously described.[13] The tests were carried out with dietary restrictions (no red meat, fresh fruit, iron preparations, vitamin C, aspirin, or other non-steroidal antirheumatics during 3 days before samples were taken), but the completed slides were not rehydrated. Participants were asked to provide two faecal samples from each of three consecutive stools. Completed tests were sent to the Department of Clinical Chemistry, Odense University Hospital, Denmark, and were processed by three technicians. Individuals with positive tests (one or more blue slides) were invited for interview, physical examination, and full colonoscopy. A double-contrast barium enema was offered when full colonoscopy could not be obtained.

We sent invitations to participants in the screening group; two reminder letters were sent during the initial screening round and a further reminder was sent during the following four screening rounds. Each screening round took 1 year to complete.

Only individuals who agreed to take part in the first screening round were invited for further screening. The protocol automatically excluded from invitation people who died or had CRC or adenomas detected between randomisation and the first screening invitations. However, these individuals were included in the follow-up analyses. All analyses were intention to treat.

	Screening rounds				
	1	2	3	4	5
Positive tests					
Number of individuals	215	159	151	200	261
% of population tested	1·0	0·8	0·9	1·3	1·8
Investigations undertaken after positive test					
Complete colonoscopy	180	142	124	168	213
Incomplete colonoscopy and DCBE	12	5	15	16	17
Incomplete colorectal examination	17	7	8	10	16
No colorectal examination	6	5	4	6	15
Colorectal carcinoma					
Number of cases	37	13	24	21	25
Predictive value (%) of positive FOB test	17	8	16	11	10
Adenoma ⩾10 mm					
Number of cases	68	61	41	44	56
Predictive value (%) of positive FOB test	32	38	27	22	21

DCBE=double-contrast barium enema.

Table 3: **Screening-group individuals who underwent further investigations after a positive FOB test and predictive value of a positive test for neoplasia**

	Screening group					Controls
	Positive test	Before invitation*	Non-responders†	Interval cancers‡	Total	
Stage of CRC						
Dukes' A	48	5	21	31	105 (22%)	54 (11%)
Dukes' B	43	9	66	46	164 (34%)	177 (37%)
Dukes' C	19	1	35	35	90 (19%)	111 (23%)
Distant spread	8	3	60	27	98 (20%)	114 (24%)
No classification	2	0	13	9	24 (5%)	27 (5%)
Total CRC	120	18	195	148	481	483
Adenoma ≥10 mm	270	7	39	97	413	174

*Had CRC diagnosed or died after randomisation but before first invitation. †Invited to first round but did not respond. ‡Had a negative FOB test at first screening round but had a diagnosis of CRC made between screenings (includes two patients who refused further examination after a positive test).

Table 4: **Stage of CRC and presence of large adenomas in screening and control groups between August, 1985, and August, 1995**

Incidence and mortality rates were calculated as the number of cases of CRC divided by the total time of observation. Between August, 1985, and August, 1995, all participants were considered to be at risk of CRC; after this period, or in the event of death, the screening status of all participants who were followed up was assessed. No interim assessments were done. We used control-group data as the denominator to calculate relative incidence and mortality rates of CRC. 95% CI values were calculated by the multiplicative poisson model. Poisson models were compared by the likelihood ratio test. Cumulative survival was calculated by the life-table method and compared by the log-rank test. Proportions were compared by the χ^2 test.

The study was approved by the regional ethics committee, and the population registers were approved by the registry board of Funen.

Results

The groups were well matched in terms of age and sex at the initial screening (table 1). The age and sex distributions of the groups did not change substantially during the study. The study profile shows overall patient numbers during the 10-year study (figure 1). 205 people died between randomisation and planned invitation for screening. Of the 49 402 people who were alive at the end of the follow-up, 1145 had moved away from Funen and six had emigrated from Denmark. The number of individuals who completed the FOB test at each screening is shown in table 2. 14 203 participants completed five screening rounds. During the first round of screening, the proportion of positive tests ranged from 0·6% to 1·7% according to age and sex; the proportion was higher in men than in women and in the elderly than in the younger participants. During the second and third screening rounds, the proportion of positive tests decreased (0·5%–1·3% and 0·5%–1·5%). However, during the last screening round, after 10 years of follow-up, the proportion of positive tests increased substantially (1·2–4·6%); the proportion of positive tests was highest in individuals older than 79 years (2·8% in women, 4·6% in men).

More than 85% of those with positive tests underwent full colonoscopy (table 3). The predictive value of a positive FOB test for detection of CRC ranged from 17% in the first screening round (37 cases among 215 positive), to 9% at the final screening (25 cases among 261 positive tests). The predictive values of a positive test for detection of large adenomas ranged from 32% at the first round to 21% at the final round (table 3).

The distribution of stages of CRC during the 10-year study is shown in table 4. None of the participants with adenomas of 10 mm or more had CRC, but some had additional smaller adenomas.

The proportion of stage A CRC was significantly lower in the control group than in the screening group (11 *vs* 22%, p<0·01), whereas the proportion of more advanced CRC (stage C, distant spread, and no classification) was significantly higher in the control group than in the screening group (table 4). Local surgery, including polypectomy for CRC, was done in 49 (10%) of the 481 screening-group participants and in 24 (5%) of the 483 controls (p<0·01). Curative surgery was achieved in 331 patients in the screening group and in 287 controls (p<0·01).

Of the 30 967 individuals in the screening group, 24 739 were alive on Aug 1, 1995, compared with 24 663 of the 30 966 controls. We obtained certificates for all participants who died in Denmark. The distribution of causes of death other than CRC was similar in both groups (table 5). There were 33 suicides in the screening group and 41 in the control group; none of these individuals had CRC.

Cause of death	Number of people in screening group (n=6228)	Number of people in control group (n=6303)
Cardiovascular disease	2497 (40·1%)	2443 (38·8%)
Lung disease	614 (9·9%)	623 (9·9%)
Other benign disease and trauma	824 (13·2%)	779 (12·4%)
Malignant disorders other than CRC	1624 (26·1%)	1721 (27·3%)
Unknown	464 (7·4%)	488 (7·7%)
CRC	182 (2·9%)	230 (3·6%)
Complications arising from treatment of CRC	23 (0·4%)	19 (0·3%)

Table 5: **Causes of death in screening and control groups between August, 1985, and August, 1995**

	Screening group	Control group
Observation time in years	281 883	281 328
CRC		
Number of patients	481	483
Incidence rate (per 1000 person-years)	1·71	1·72
Incidence ratio (95% CI)	1·00 (0·87–1·13)	..
Death from CRC		
Number of deaths	182	230
Mortality rate	0·65	0·82
Mortality ratio (95% CI)	0·79 (0·65–0·96)	..
Death from CRC and complications from treatment		
Number of deaths	205	249
Mortality rate	0·73	0·89
Mortality ratio (95% CI)	0·82 (0·68–0·99)	..
Death from all causes		
Number of deaths	6228	6303
Mortality rate	22·09	22·40
Mortality ratio (95% CI)	0·99 (0·95–1·02)	..

Controls are the reference group.

Table 6: **Incidence and mortality rates for CRC between August, 1985, and August, 1995**

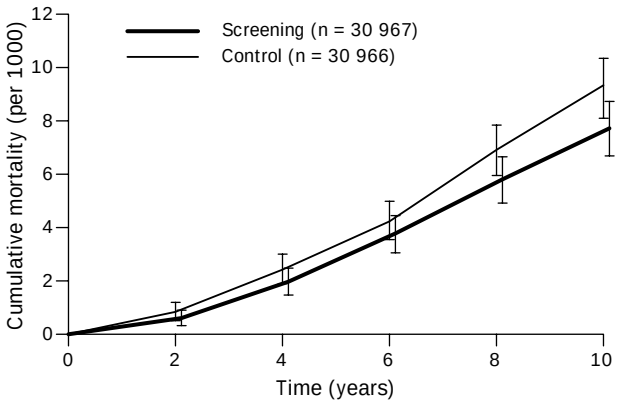

Figure 2: **Biennial cumulative mortality rates for CRC including deaths attributable to complications from CRC**
Vertical bars=95% CI.

After the first screening, the difference in CRC incidence rates between the groups grew smaller and at 10 years the cumulative incidence of CRC was similar (table 6). By contrast, the cumulative CRC mortality rate was significantly higher in controls than in screening-group participants, irrespective of whether complications arising from treatment for CRC were excluded.

The ratio of CRC mortality rates in screening and control groups was significantly less than 1·0 (table 6, figure 2). Mortality rates for all causes of death did not differ significantly between the groups. The necropsy rate was 24% in both groups. The CRC mortality ratio, which included deaths attributable to complications from CRC treatment was: 0·80 (95% CI 0·61–1·02) in men; 0·85 (0·64–1·11) in women; 0·84 (0·68–1·05) in individuals 60 years or older at start of follow-up; and 0·77 (0·54–1·10) in those younger than 60 years. In the screening group, the mortality ratios for left-sided cancer (rectum and sigmoid) and cancer in the remaining colon were 0·87 (0·69–1·09) and 0·72 (0·52–0·98), respectively.

The cumulative survival of patients with CRC is shown in figure 3. The survival rate was higher in patients with screen-detected CRC than in controls (log-rank test $p<0·01$). Non-responders had the lowest survival rate of all subgroups and controls ($p=0·12$). Interval cases of CRC had a higher survival rate than controls ($p=0·05$). The overall cumulative survival in patients with CRC was significantly higher in the screening group than in the control group ($p<0·01$). Within stages of CRC, no significant difference was found in cumulative survival between the screening group and controls, but screening-group patients with Dukes' stage A tumours tended to have a better survival than those in the control group ($p=0·13$).

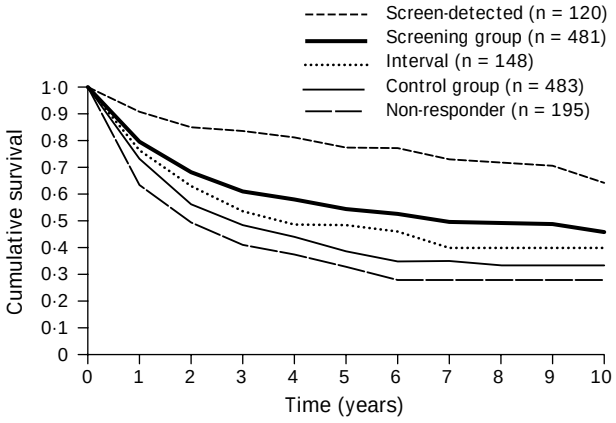

Figure 3: **Cumulative survival in screening (by subgroups) and control groups**
Subgroup of patients who died or had CRC diagnosed between randomisation and first invitation omitted.

Discussion

We found that after 10 years of follow-up, screening by FOB every 2 years (Hemoccult-II without rehydration) led to a reduction of 18% in CRC mortality, which was independent of sex and age, in individuals aged 45–75 years. Of the 20 672 participants who were screened at least once only 892 (4·3%) underwent colonoscopy. Our findings contrast with those of the Minnesota study,[4] in which 38% of people who were screened annually during a period of 13 years had colonoscopy (with an intermission of 3 years), and even after biennial screening 28% had at least one colonoscopy; but there was no significant reduction in mortality from CRC. Our study was truly representative of the general population. Our findings can, therefore, be extrapolated to general population screening. By contrast, the Minnesota study included only volunteers with a low CRC mortality.

In this study, mortality from causes other than CRC was similar in the screening and control groups, which suggests that comparability was achieved by randomisation. The finding that mortality attributable to complications from CRC treatment was similar in the groups was unexpected, particularly because more patients had local surgery in the screening group than in the control group. However, the number of deaths was small—23 and 19, respectively—and we believe that this finding may be due to chance.

Although annual screening might reduce the present high rate of interval cancers, it would also increase costs and the proportion of false-positive FOB results. Nevertheless, even if we used annual screening and increased the rate of colonoscopies from 4·3% to 8·6%, this rate would be less than a quarter that of the Minnesota study, due to the lower rate of positive tests with the Hemoccult-II test without rehydration used at Funen. The 18% reduction in mortality from CRC reported here would prevent 360 of the 2000 deaths from CRC in Denmark per year. Colonoscopic expertise and economic resources for screening with rehydrated Hemoccult-II are not currently available in Denmark. Although annual screening with the unhydrated test is a possibility, such screening should be introduced only after further studies have been done and more data on side-effects and cost are available.

False-negative tests can lead to a delay in presentation and in subsequent treatment, but in our study patients with interval cancers had a higher survival rate than controls. This finding may reflect earlier diagnosis of CRC rather than later death (lead-time bias). The rate of interval cancers might be reduced by the introduction of annual screening.

The difference in rates of death from CRC increased between the groups over time. The slight difference in mortality at 10 years means that this study needs to be continued; screening rounds 6 and 7 will be carried out throughout 1996 and 1997 to assess compliance for repeated screenings and the effect of increasing age. Economic analyses of cost per life-year saved are also in progress.

The finding that screening led to a smaller reduction in mortality from rectal and sigmoid cancer than from cancers of the upper colon supports the recommendations for screening trials that include flexible sigmoidoscopy.

The removal of precursor adenomas in 413 screening-group participants compared with 174 controls did not affect CRC incidence in the screening group. The adenoma-carcinoma sequence may have a duration of several years and any reduction in CRC incidence because of polyp removal during colonoscopy will be investigated in the forthcoming years of our study.

In conclusion, biennial screening with Hemoccult-II in individuals aged 45–75 years reduced CRC mortality after 10 years of follow-up and five screening rounds. CRC is common among elderly people, and the reduction in mortality achieved by FOB screening cannot currently be achieved by any other known preventive measure. Better screening methods may become available in the future, but until then, screening by FOB tests is a feasible option.

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