Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: A randomized clinical trial

Øyvind Holme, MD[1,2,3,*], **Magnus Løberg, MD**[2,3,4,*], **Mette Kalager, MD, PhD**[2,3,5], **Michael Bretthauer, MD, PhD**[1,2,3,4], **Miguel A. Hernán, MD, DrPH**[3], **Eline Aas, PhD**[2], **Tor J Eide, MD, PhD**[7], **Eva Skovlund, PhD**[8], **Jørn Schneede, MD, PhD**[9], **Kjell Magne Tveit, MD, PhD**[10,11], and **Geir Hoff, MD, PhD**[2,5,6]

[1]Sorlandet Hospital Kristiansand, Dep of Medicine, Kristiansand, Norway

[2]Insitute of Health and Society, University of Oslo, Oslo, Norway

[3]Harvard School of Public Health, Departments of Epidemiology and Biostatistics; Harvard-MIT Division of Health Sciences and Technology, Boston, MA, USA

[4]Oslo University Hospital, Dep. of Transplantation Medicine, Oslo, Norway

[5]Telemark Hospital Skien, Skien, Norway

Corresponding author: Øyvind Holme, Sorlandet Hospital Kristiansand, Postboks 416, 4604 Kristiansand, Norway, oyvind.holme@sshf.no. Fax: +47 38073709. Phone: +47 38073000.
[*]These authors contributed equally

[6]Cancer registry of Norway, Oslo, Norway

[7]Oslo University Hospital, Dep of Pathology, Oslo, Norway

[8]School of Pharmacy, University of Oslo, Norway

[9]Department of Pharmacology and Clinical Neuroscience, Clinical Pharmacology unit, Umeå University, Umeå, Sweden

[10]Department of Oncology, Oslo University Hospital, Oslo, Norway

[11]University of Oslo, Oslo, Norway

Abstract

Importance—Colorectal cancer is a major health burden. Screening is recommended in many countries.

Objective—Estimate the effectiveness of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality in a population-based trial.

Design—Randomized controlled trial in individuals aged 50–64 years. Screening was performed in 1999–2000 (55–64 year age-group) and 2001 (50–54 year age-group). End of follow-up: Dec 31st 2011.

Setting—Population of Oslo city and Telemark County, Norway.

Participants—100,210 individuals were identified in the screening areas. 1,415 individuals were excluded due to prior colorectal cancer, emigration, or death. Three individuals could not be traced in the population registry.

Intervention—Individuals randomized to the screening group were invited to screening. Within the screening group, individuals were randomized 1:1 to once-only flexible sigmoidoscopy or combination of once-only flexible sigmoidoscopy and fecal occult blood-testing (FOBT). Individuals with positive screening test (cancer, adenoma, polyp ≥ 10 mm, or positive FOBT) were offered colonoscopy. The control group received no intervention.

Main outcome measures—Colorectal cancer incidence and mortality.

Results—98,792 individuals were included in the intention to screen analyses; 78,220 in the control group and 20,572 in the screening group (10,283 randomized to flexible sigmoidoscopy and 10,289 to flexible sigmoidoscopy and FOBT). Compliance with screening was 63%. After median 10.9 years, 71 individuals had died from colorectal cancer in the screening group, and 330 in the control group (31.4 vs. 43.1 deaths, absolute rate difference 11.7 (95% CI 3.0–20.4) per 100,000 person-years); hazard ratio [HR] 0.73 (95% confidence interval [CI] 0.56–0.94). Colorectal cancer was diagnosed in 253 individuals in the screening group, and 1,086 in the control group (112.6 vs. 141.0 cases, absolute rate difference: 28.4 (95% CI 12.1–44.7) per 100,000 person-years); HR 0.80 (95% CI 0.70–0.92). Colorectal cancer incidence was reduced in both the 50–54 year age-group (HR 0.68; 95% CI 0.49–0.94) and the 55–64 year age-group (HR 0.83; 95% CI 0.71–0.96). There was no difference between the flexible sigmoidoscopy only and the flexible sigmoidoscopy/FOBT screening groups.

Conclusion and relevance—In Norway, once-only flexible sigmoidoscopy screening or flexible sigmoidoscopy and FOBT reduced colorectal cancer incidence and mortality on a population level compared with no screening. Screening was effective both in the 50–54 and the 55–64 year age-group.

Trial registration—ClinicalTrials identifier NTC00119912, http://clinicaltrials.gov

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide.[1] Most CRC cases develop from adenomas.[2] Removal of adenomas by colonoscopy or flexible sigmoidoscopy has therefore been endorsed as a primary prevention tool for CRC.[3,4]

Recently, results from three large randomized trials comparing flexible sigmoidoscopy screening with no screening showed reductions in CRC incidence (by 18–23%) and CRC mortality (by 22–31%).[5–7] However, these trials had some limitations. First, they only included individuals aged 55 years and older, while US guidelines recommend starting screening at age 50.[3] Second, the trials were not population-based and included only volunteers, which might have resulted in estimates that do not reflect the effectiveness of national screening programs with similar compliance. Last, prior trials were partly conducted in settings in which CRC screening outside the trial was available to the no-screening group, which may result in attenuated effect estimates. The ideal scenario to overcome these problems is a population-based randomized trial with no screening outside the trial in individuals aged 50 years and older.

The Norwegian Colorectal Cancer Prevention Trial (NORCCAP) is such a randomized trial. Eligible individuals aged 50 to 64 years were randomized directly from the Norwegian Population Register to screening with flexible sigmoidoscopy or no screening (care as usual in Norway during the trial period). Preliminary trial findings showed no reduction in CRC incidence or mortality after seven years of follow-up.[8] Here, we report incidence and mortality of colorectal cancer after 11 years of follow-up.

Methods

In November 1998, all men and women aged 55–64 years living in the City of Oslo or Telemark County, Norway, were identified through the Norwegian Population Register. Equal numbers of men and women were randomly sampled from the birth cohorts of 1935–1945 and invited by mail for screening (screening group). Remaining individuals in the screening areas constituted the control group; controls were never contacted and were not offered any screening. Individuals in the screening group were further randomized (1:1) to receive an invitation for once only flexible sigmoidoscopy, or a combination of once only flexible sigmoidoscopy and immunological fecal occult blood testing (FOBT) (FlexSure OBT, Beckman-Coulter, Palo Alto, CA, USA). An independent body performed both randomization procedures using computerized algorithms. At the end of year 2000, the study funding bodies (Norwegian Government and Norwegian Cancer Society) decided to extend the study to also include all individuals aged 50–54 years in the same geographic areas to obtain more information about the ideal age to start screening. No power calculations were

employed for this extension of the trial. The randomization, invitation and screening procedures were similar to the 55–64 year age group. Due to higher birth rates in the 50–54 year age group (born 1946–1950, after World War II), the ratios between the screening and control group were 1:3 in the 55–64 year age group and 1:5.4 in the 50–54 year age group. The screening interventions took place in 1999 and 2000 for the 55–64 year age group, and in 2001 for the 50–54 year age group. During the course of the trial, there was no CRC screening program in Norway, and there has been virtually no screening colonoscopies outside the trial.[9] Thus, all cases of CRC in the control group were identified by work-up of gastrointestinal symptoms.

The study entry date for individuals in the screening group was the date of the screening examination as proposed in their invitation letter. For the control group, each individual was assigned an entry date evenly distributed throughout the screening period (January 1st 1999 to December 31st 2000 for the 55–64 year age group; January 1st 2001 to December 31st 2001 for the 50–54 year age group). The only exclusion criterion was prior history of CRC. We did not have any information on family history of CRC at the time of the random sampling. Details of the study design, baseline findings, and short-term follow-up have been published previously.[8,10,11] All participants who attended the screening examination provided written, informed consent. The study was approved by the Ethics Committee of South-East Norway and the Norwegian Data Inspectorate.

All screening examinations were performed at three dedicated centers, two in Telemark and one in Oslo. Bowel cleansing was restricted to a 240 milliliter Sorbitol enema administered on attendance at the screening center. All examinations were performed using standard colonoscopes (140cm Olympus colonoscopes, Olympus Europa GmbH, Hamburg, Germany) with the exception of a small screening center in Telemark, where a disposable endoscopy sheath was used (Vision Sciences 60 cm disposable Endosheath, Vision Sciences, Natick, MA, USA). During flexible sigmoidoscopy, all visible lesions were biopsied and subjected to histopathological evaluation. The screening participant brought the FOBT to the screening center and the test was analyzed on-site prior to flexible sigmoidoscopy. There was no option to be screened with FOBT only. Persons with a positive screening test, defined as any polyp   10 mm (irrespective of histology), any adenoma, CRC, or positive FOBT, were referred for colonoscopy at the screening centers. During colonoscopy, all lesions were removed. Designated pathologists examined all specimens. Post-polypectomy surveillance recommendations followed Norwegian guidelines.[12]

The primary study endpoints were CRC incidence and mortality. We also analyzed incidence and mortality from CRC located distal and proximal to the descending-sigmoid junction, stage-specific incidence, and all-cause mortality. All residents in Norway are assigned a unique personal identification number, and all included individuals were followed through linkage to public registries. Date of diagnosis, stage, and localization of colorectal cancer was obtained from the Cancer Registry of Norway (near complete registration of all cancers in Norway).[13] Colorectal cancer was defined as adenocarcinoma of the colon or rectum and classified as localized (Dukes A or B) or advanced (Dukes C or D). Cases were also included if they were reported to the Cancer Registry as clinically

diagnosed CRC without confirmatory histology (14 cases). Date and cause of death was obtained from the Cause of Death Registry. Socioeconomic data of all individuals was obtained from Statistics Norway.

Statistics

The power calculation was conducted for the 55–64 year age group and for the two screening groups combined versus the control group. [8] Assuming 70% compliance, and 30% intention-to-treat reduction in CRC incidence after 5 years with 90% power, and a significance level of 5%, 14,000 individuals had to be included in the screening group and 42,000 in the control group. Half of the individuals in the screening group were offered flexible sigmoidoscopy screening only, and the other half screening with flexible sigmoidoscopy and FOBT (the effectiveness comparison of the two different screening groups was a secondary analysis).

Our primary analytic approach followed the intention-to-screen principle. Each individual was followed from entry date until diagnosis of colorectal cancer, death, emigration, or December 31st 2011, whichever occurred first. We computed age-standardized rates, with the screening group as the standard, to adjust for a slightly higher mean age in the screening group than in the control group (56.9 vs. 56.1 years). We also estimated age-adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) for the screening group versus the control group by fitting Cox models adjusted for age. We performed two sensitivity analyses: The ratio between the control group and screening group was higher in Oslo (6.2:1) than in Telemark (1.5:1) due to higher population numbers in Oslo. The age-adjusted CRC incidence and mortality rates, however, were comparable in the control groups in both areas. Consequently, in a sensitivity analysis when we included screening center in the Cox model, the results were unchanged. We also performed analyses with follow-up restricted to 11 years in both screening and control group to take into account the slightly different follow-up time (which was due to age differences), with comparable results.

To test for heterogeneity, we included product ("interaction") terms (between sex and study group and between age-group and study group) in the Cox model. We computed age-standardized cumulative probability of CRC incidence and mortality. Further, we calculated the yearly age-standardized risk ratios after randomization in the screening group and screening compliers relative to the control group. The number needed to invite for screening to prevent one CRC case or death within 10 years was calculated as the inverse of the age-standardized risk difference at 10 years (all individuals were followed for at least 10 years). We estimated the incremental cost-effectiveness ratios (ICER) expressed in terms of prevented CRC-cases and CRC-deaths over ten years by comparing no screening to screening of the two age-groups (50–54 versus 55–64) separately and overall. Costs of screening, treatment, and follow-up were based on UK data with NICE's recommended discount rate of 3.5%.[14,15] All numbers were adjusted to 2013 level using the UK Consumer Price Index and reported in US$[16]. (See Supplementary appendix).

As a secondary analytic approach, we estimated a per protocol effect that measures the effect of the intervention adjusted for noncompliance (see supplementary appendix for details).[17,18] We used instrumental variable estimation with randomization group as the

instrument to estimate the per protocol 10-year risk differences of CRC mortality and incidence for screening versus no screening via two-stage least-squares estimation. We focused on the 10-year risk difference because all individuals were followed for at least 10 years. All analyses were conducted with STATA 13.0 software (StataCorp, College Station, Texas, USA).

Results

Of 100,210 randomized individuals, 1,415 (1.4%) were excluded due to diagnosis of CRC, death, or emigration before study entry (Figure 1) and three persons could not be traced through the population register. Thus, our analyses include 78,220 individuals in the control group and 20,572 individuals in the screening group. A total of 10,283 individuals were randomized to flexible sigmoidoscopy screening only and 10,289 individuals were randomized to be screened with flexible sigmoidoscopy and FOBT. Baseline characteristics are displayed in Table 1. End of follow-up was Dec 31st 2011.

Of 20,572 individuals invited to screening, 12,955 (63%) attended the screening examination. Compliance was 60.9 % in the combined screening group and 65.1% in those invited for flexible sigmoidoscopy screening only (p<0.001). Screening findings and key endoscopy figures are displayed in table 2. There were no complications after flexible sigmoidoscopy. A total of 2,816 colonoscopies were performed in 2,520 individuals (19.5% of those who attended screening). Perforation occurred during colonoscopy in six individuals, and four individuals were admitted to hospital for post-polypectomy bleeding following snare polypectomy. Two patients had complications after surgery. No screening-associated deaths occurred.

Colorectal cancer incidence

Median follow-up was 11.2 years in the screening group and 10.9 years in the control group. The age-standardized CRC incidence rate (per 100,000 person-years) was 112.6 in the screening group and 141.0 in the control group, absolute rate difference: 28.4 (95% CI 12.1–44.7), and the HR was 0.80 (95% CI 0.70–0.92) (Table 3; Figure 2). The corresponding HR was 0.68 (95% CI 0.49–0.94) in the 50–54 year age group, and 0.83 (95% CI 0.71–0.96) in the 55–64 year age group (P-value for heterogeneity: 0.3). The HR was 0.73 (95% CI 0.60–0.89) in men and 0.87 (95% CI 0.72–1.06) in women (P-value for heterogeneity: 0.3). The HR was 0.76 (95% CI 0.63–0.92) for distal CRC and 0.90 (95% CI 0.73–1.10) for proximal CRC. For flexible sigmoidosxopy screening only, the HR was 0.72 (95% CI 0.59–0.87), and for flexible sigmoidoscopy and FOBT, HR was 0.88 (95% CI 0.74–1.05) (P-value for heterogeneity: 0.1). Screen-detected CRC was more often diagnosed at an earlier stage than non screen-detected CRC (Table 4). The relative risk of CRC was lower each year after screening in the screening group compared to the control group except for the first year after randomization due to screen-detected cancers (Figure 3 and 4A and B). The number needed to invite for screening to prevent one CRC case over 10 years was 498 (ICER $58,448; see supplementary appendix).

Colorectal cancer mortality

The age-standardized CRC mortality rate (per 100,000 person-years) was 31.4 in the screening group and 43.1 in the control group, absolute rate difference 11.7 (95% CI 3.0–20.4), HR was 0.73 (95% CI 0.56–0.94) (Table 3). The corresponding HR was 0.74 (95% CI 0.40–1.35) in the 50–54 year age group and 0.73 (95% CI 0.55–0.97) in the 55–64 year age group. The HR was 0.58 (95% CI 0.40–0.85) in men and 0.91 (95% CI 0.64–1.30) in women (P-value for heterogeneity: 0.1). The HR was 0.79 (95% CI 0.55–1.11) for distal CRC mortality and 0.73 (95% CI 0.49–1.09) for proximal CRC mortality (Table 3). For flexible sigmoidoscopy screening only, HR was 0.84 (95% CI 0.61–1.17), and for flexible sigmoidoscopy and FOBT, the HR was 0.62 (95% CI 0.42–0.90) (P-value for heterogeneity: 0.2). A visual inspection of Figures 2B and 3 suggests that CRC mortality started to diverge in the two groups after 9 years of follow-up. The number needed to invite for screening to prevent one CRC death over 10 years was 1,547 (ICER $226,002; see supplementary appendix).

There were no differences in all-cause mortality between the screening and control group HR 0.97 (95% CI 0.93–1.02).

Compliance-adjusted analysis (per protocol effect)

The intention to screen 10-year risk absolute difference (risk in screening group minus risk in control group) was −0.22% (95% CI −0.38% to −0.06%) for CRC and −0.06% (95% CI −0.14% to 0.03%) for CRC-death in the entire study population. After adjustment for noncompliance, the corresponding 10-year risk differences were −0.42% (95% CI −0.69% to −0.15%) and −0.10% (95% CI −0.25% to 0.05%), respectively. See Appendix for details.

Discussion

In this study, flexible sigmoidoscopy screening reduced CRC incidence by 20% and CRC mortality by 27%. Younger individuals aged 50–54 years seem to benefit at least as much from the screening intervention as older individuals aged 55–64 years.

Three other large randomized trials of flexible sigmoidoscopy screening with comparable length of follow-up have been published. In the trials from the UK (Flexi Scope trial) and Italy (SCORE), offering once only flexible sigmoidoscopy examination to people aged 55–64 years, CRC incidence was reduced by 23% and 18% and CRC mortality by 31% and 22%, respectively.[5,7] In the PLCO trial from the US, including individuals aged 55–74 years offering flexible sigmoidoscopy screening at two occasions, CRC incidence was reduced by 21% and CRC mortality by 26%.[6]

Our results are in accordance with those reported from the previous trials and extend them in three important ways. First, unlike the other trials, our estimates were not affected by screening contamination in the control group. Second, our population-based design with random sampling directly from the population registry allows estimation of the effectiveness of a national screening program with similar compliance. The study populations of the other trials consisted of volunteers. Therefore, their findings may not be generalizable to their national populations if those included in the trial had a different risk of CRC diagnosis or

death than the background population. Indeed, in the Italian SCORE trial, the CRC mortality rate was 46% lower in the control group than in the background population.[7] Third, our estimates show, for the first time, the effectiveness of screening in individuals aged 50–54 years.

The ideal age to start screening for CRC has not been firmly established, and national screening recommendations vary accordingly.[19] Until now, no study has reported on effectiveness of flexible sigmoidoscopy screening under the age of 55. We show that individuals aged 50–54 benefit as much from flexible sigmoidoscopy screening as those older than 55 years with respect to CRC incidence.

The four flexible sigmoidoscopy trials had important differences in the threshold for referral to colonoscopy. In the present study, we adapted a low referral threshold, meaning that any adenoma (irrespective of size) qualified for colonoscopy. The PLCO trial referred all individuals with any detected lesion or polyp to follow-up, while only people with advanced or multiple adenomas were offered colonoscopy in the UK trial. The Italian trial adopted the recommendation from the UK trial, but in addition referred individuals with adenomas 6–9 mm in size. These differences led to widely varying colonoscopy rates (19.5% in NORCCAP; 5.0% in UK; 7.8% in Italy; 21.9% in US trial, respectively).[6,20,21] Despite these differences, reported reductions in CRC incidence were similar (18–23%).[5–7] This observation may infer that the least extensive referral approach could be sufficient, implying that only individuals with advanced adenomas at flexible sigmoidoscopy should be referred to colonoscopy.

Adaption of this recommendation would have great impact on costs of flexible sigmoidoscopy screening programs, but would also reduce the number of advanced adenomas detected in the proximal colon. We have previously reported that the number of colonoscopies would have been reduced by 66% if only participants in the NORCCAP trial with advanced adenomas were referred to colonoscopy. But, as a consequence, 38% of patients with proximal advanced adenomas would not have been detected.[22] Other trials have confirmed that about half of proximal advanced adenomas did not have a synchronous distal lesion, and would thus have been missed due to normal findings at flexible sigmoidoscopy.[23,24] In our trial, we found a 10% reduction in proximal CRC incidence, which is in accordance with the PLCO trial in which a 14% reduction in proximal CRC incidence was found with a similar colonoscopy referral rate. The optimum threshold for colonoscopy referral in a screening program should be weighted against costs and available endoscopy resources.

Adding one-time FOBT did not lead to additional screen-detected cancers or the detection of more advanced adenomas. This is in keeping with previous results.[25] To reduce CRC mortality, FOBT has to be repeated.[26–28] In fact, the combined screening approach led to lower compliance in our trial and could thus have a negative impact on a screening program. No reduction in all-cause mortality was observed. This was not unexpected, as only 4% of all deaths in the NORCCAP population were due to CRC and the trial was not powered to detect any difference in all-cause mortality.

Even if underpowered for subgroups analyses, our results may suggest a stronger effect of the screening intervention in men than in women. CRC incidence and mortality was reduced by 27% and 42% in men and 13% and 9% in women, respectively. A larger benefit for men was also evident in the PLCO and the UK trials.[5,6] Possible explanations, supported by previous studies, may be that more women than men have proximal advanced adenomas without distal lesions which would have triggered a full colonoscopy, and more women than men have proximal sessile serrated lesions which may be more difficult to detect.[29–31]

In this paper we use observed data for prevented CRC incidence and CRC-deaths as a measure for clinical cost-effectiveness in a ten-year perspective. Hence, our findings are not comparable to most other cost-effectiveness analyses which are model-based and apply a lifetime perspective.[32] Our estimate of the costs per prevented CRC shows that screening in the 50–54 year age group is at least as cost-effective as in the 55–64 year age groups, despite lower baseline risk of CRC (Supplementary appendix).

Estimating the per-protocol effect under full adherence is important to quantify the maximum benefit of the screening intervention that may be achieved in a screening program. Our results show that, in case of full compliance, the absolute reduction in 10-year CRC risk would be twice as high as in the intention-to-treat analysis (−0.42% versus −0.22%) if the compliers were approximately representative of the general population. The CRC incidence rate in non-compliers was equal to that in the control group (eFigure 1), which supports the generalizability of these estimates to the entire population. Figure 4 A and B approximately quantifies the effectiveness of a flexible sigmoidoscopy screening program on CRC incidence under perfect compliance.

A possible limitation of our trial is that we based mortality estimates on public registries and did not include a death review committee or expert coder to re-review death certificates. However, using a death review committee did not significantly alter the number of deaths attributable to CRC in two previous CRC screening trials.[7,33] Even if more CRC deaths were found in the UK flexible sigmoidoscopy trial by an expert coder than were obtained from public registries, the added yield was similar in both the screening and control group and therefore did not change the effect estimates of the screening intervention.[5]

Conclusion

Compared with no screening, once only flexible sigmoidoscopy screening or flexible sigmoidoscopy with faecal occult blood testing reduced CRC incidence and mortality in a population-based trial in Norway. Screening effects were similar in 50–54 and 55–64 year old individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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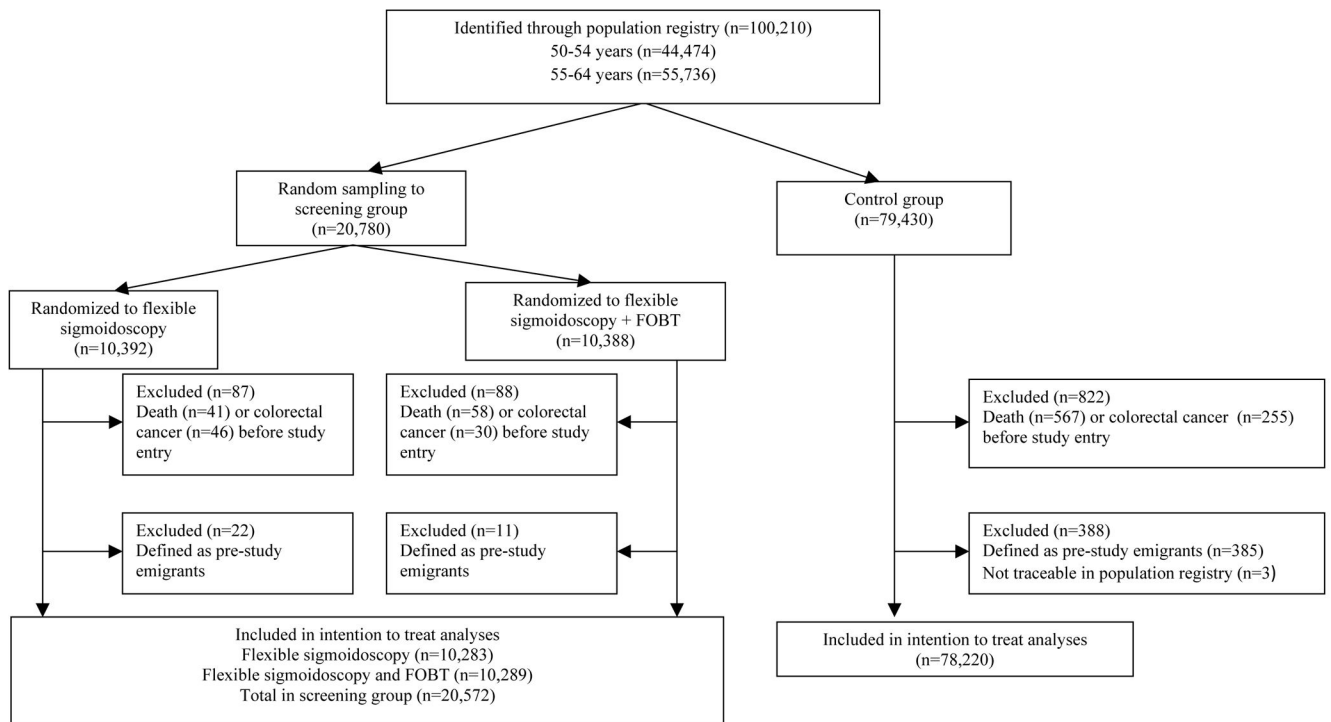
Figure 1. Flowchart. Norwegian Colorectal Cancer Prevention trial (NORCCAP)
Individuals aged 55–64 and 50–54 years were invited to screening in 1999–2000 and in 2001, respectively.

The screening examination date originally proposed in the invitation letter was considered the date of study entry for the screening group. A randomly allocated date (Jan 1st 1999 – Dec 31st 2000 for the 55–64 year age-group and Jan 1st – Dec 31st 2001 for the 50–54 year age-group) was considered the date of study entry for the control group.

Figure 2A

A: Overall colorectal cancer incidence

HR 0.80 (95% CI 0.70-0.92)

(Cumulative probability vs Years of follow-up; Control group (black), Screening group (red))

Figure 2B

B: Overall colorectal cancer mortality

HR 0.73 (95% CI 0.56-0.94)

(Cumulative probability vs Years of follow-up; Control group (black), Screening group (red))

Figure 2C

C: Distal colorectal cancer incidence

HR 0.76 (95% CI 0.63-0.92)

Figure 2D

D: Distal colorectal cancer mortality

HR 0.79 (95% CI 0.55-1.11)

Figure 2. Cumulative probability of colorectal cancer incidence and mortality
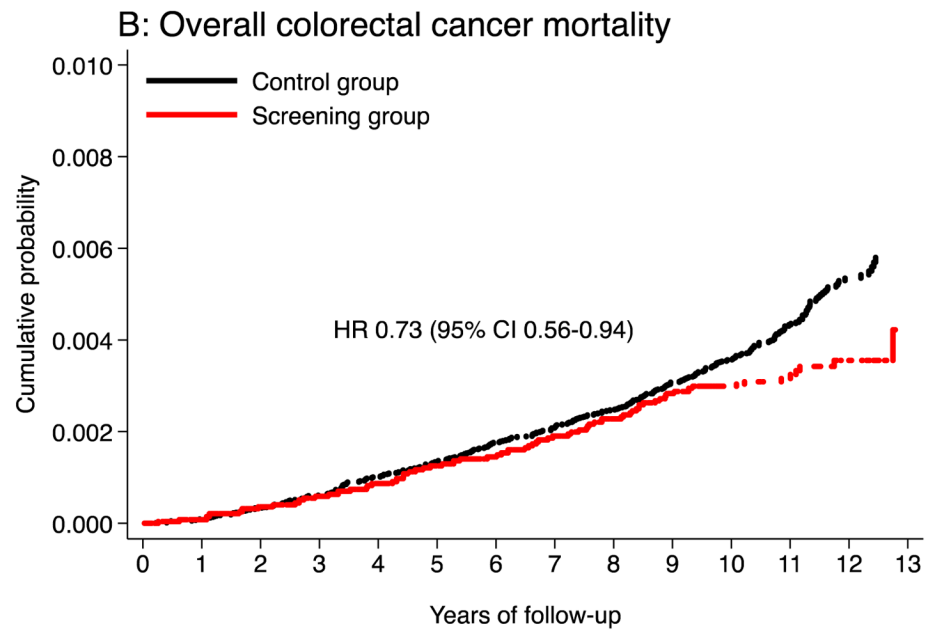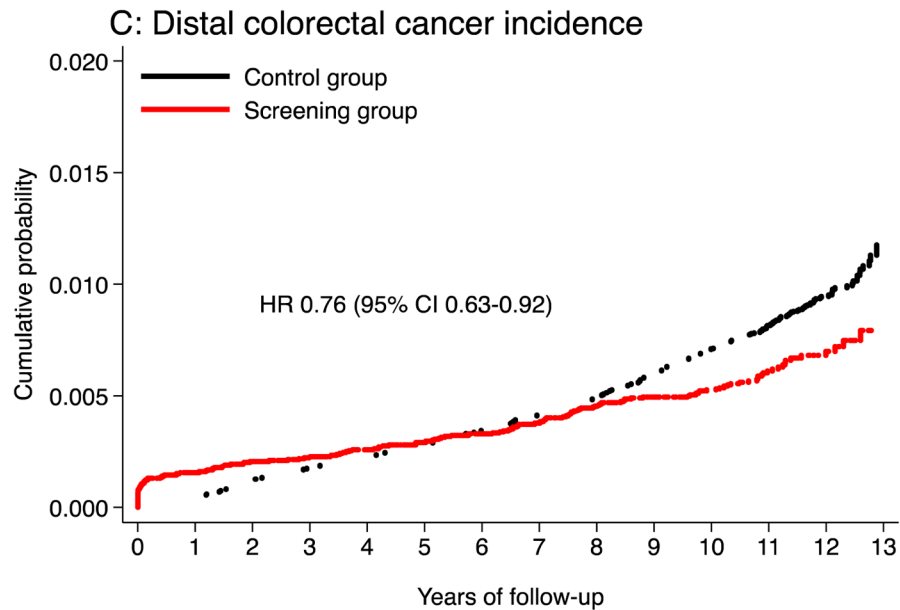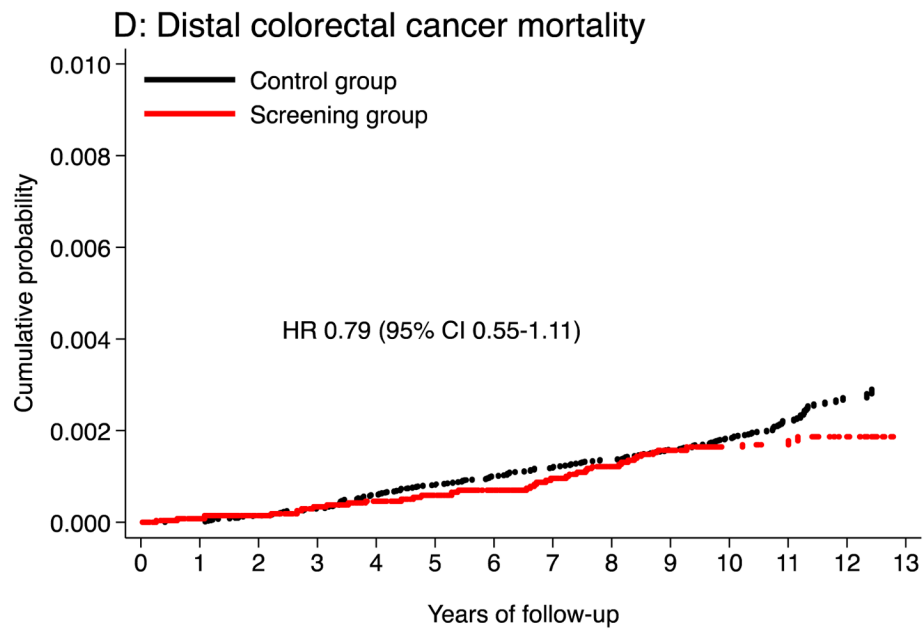The panels show cumulative probability for colorectal cancer incidence (panels A and C) and mortality (panels B and D), for the colorectum overall and for the distal colon. HR: Hazard ratio. CI: Confidence interval.

At-risk table, panel A and C

At risk							
Year	0	2	4	6	8	10	12
Screening	20572	20141	19731	19306	18808	18298	5285
Control	78220	76648	75059	73415	71598	69508	17277

At-risk table, panel B and D

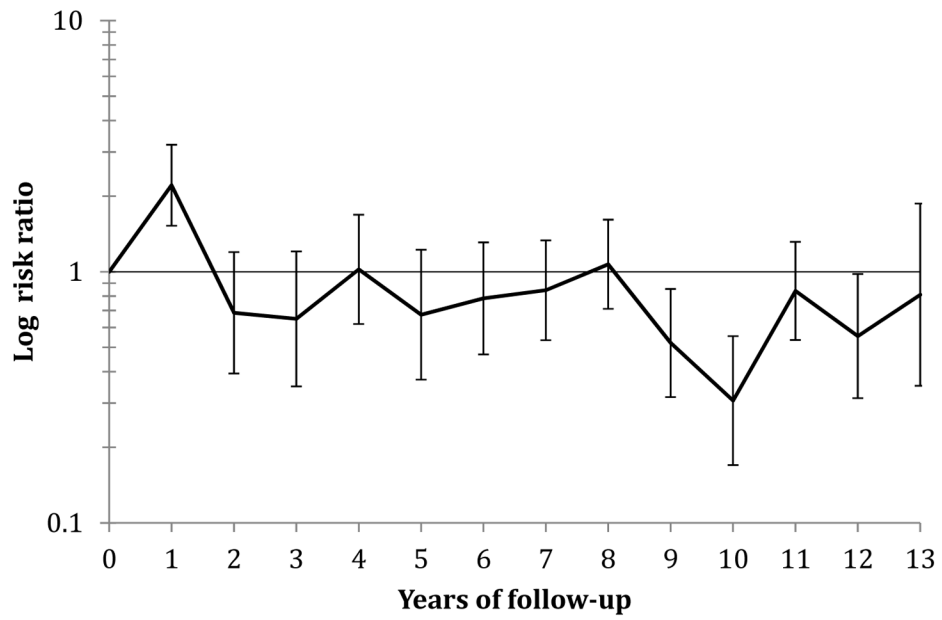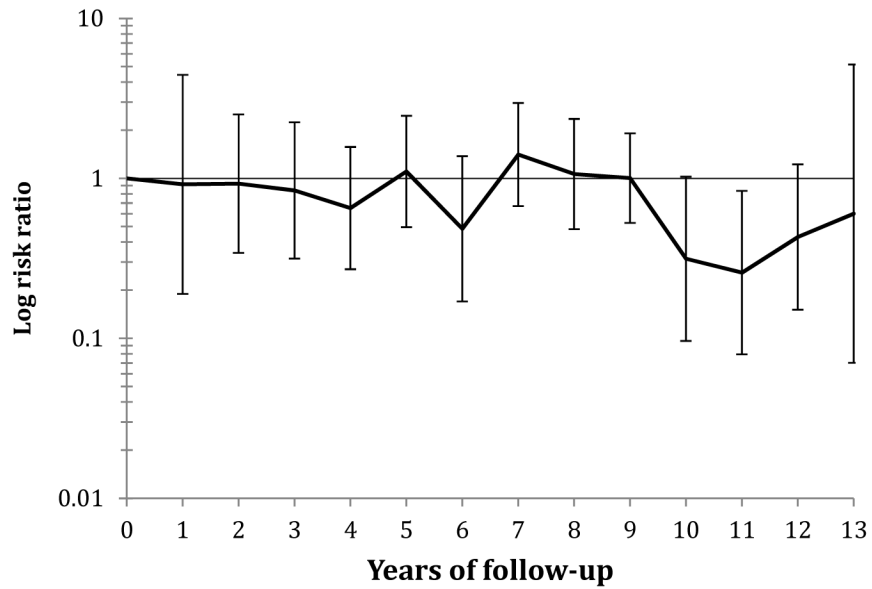| At risk							
Year	0	2	4	6	8	10	12
Screening	20572	20204	19816	19411	18945	18448	5656
Control	78220	76777	75272	73722	72044	70127	17517

Figure 3A

Figure 3B

Figure 3.
Figure 3A: Yearly risk ratio (with error bars) of CRC incidence for the screening group relative to the control group.

Figure 3B: Yearly risk ratio (with error bars) of CRC mortality for the screening group relative to the control group.

Figure 4A:

Figure 4B:

Figure 4.
Figure 4A: Yearly risk ratio (with error bars) for overall colorectal cancer incidence in screening compliers (n=12,955) and the screening group (compliers and noncompliers, n=20,572) relative to the control group (n=78,220).
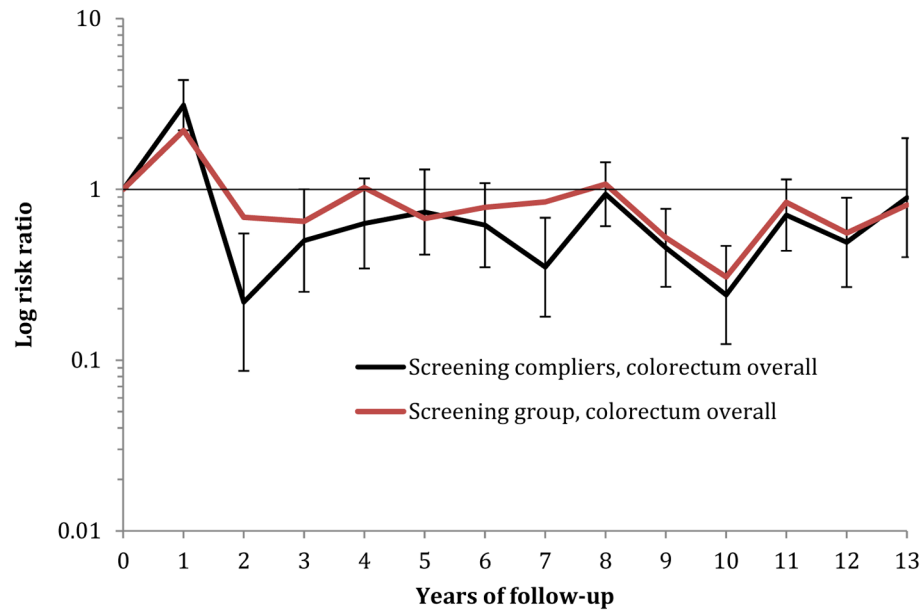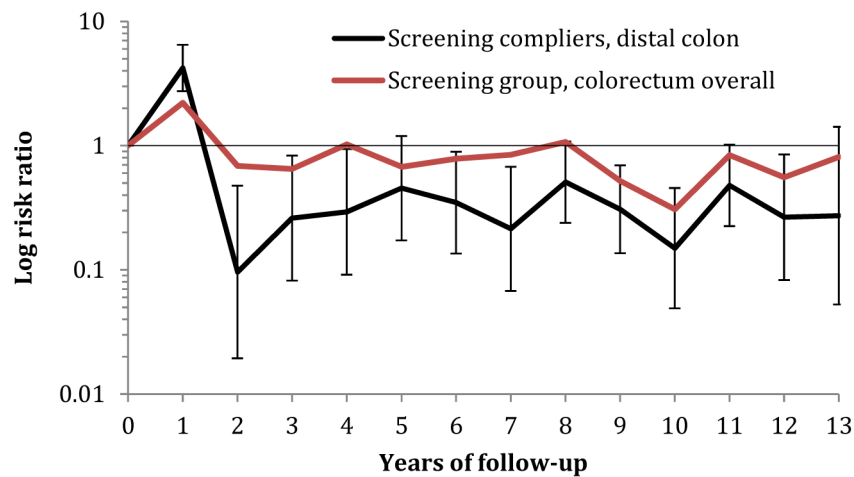Figure 4B: Yearly risk ratio (with error bars) for distal colorectal cancer incidence in screening compliers (n=12,955) and for overall colorectal cancer incidence in the screening group (compliers and noncompliers, n=20,572) relative to the control group (n=78,220).

Table 1

Baseline characteristics of the study participants

Results are given as numbers (percentages) if not stated otherwise.

	Control group (n=78,220)	Screening group (n=20,572)
Age (mean, SD)	56.1 (3.8)	56.9 (3.8)
Sex		
Men	38,922 (49.8)	10,269 (51.1)
Women	39,298 (50.2)	10,303 (49.9)
Age group		
50–54 years	37,131 (47.5)	6,920 (33.6)
55–64 years	41,089 (52.5)	13,652 (66.4)
Area of residence		
Telemark	15,176 (19.4)	10,314 (50.1)
Oslo	63,044 (80.6)	10,258 (49.9)

SD: standard deviation

Table 2

Findings at screening and endoscopy key figures

Results in numbers (percentages) which include findings at flexible sigmoidoscopy and colonoscopy of screen-positive individuals in screening-compliers.

	Flexible sigmoidoscopy (n=6,692)	Flexible sigmoidoscopy and FOBT (n=6,263)	P-value
Any adenoma[a]	1,156 (17.3)	1,054 (16.9)	0.5
Advanced adenoma[a]	304 (4.6)	278 (4.5)	0.8
Colorectal cancer	21 (0.3)	20 (0.3)	1.0
Referred for colonoscopy	1,303 (19.5)	1,336 (21.3)	0.008
Attended colonoscopy examination	1,249 (18.7)	1,271 (20.3)	0.02
Cecum intubation[b]	1,130 (90.5)	1,140 (89.7)	0.3
Number of colonscopies	1403	1413	0.2
Complications with flexible sigmoidoscopy	0	0	-
Complications with colonoscopy[c]	5	5	0.8
Recommended surveillance	670 (10.1)	598 (9.6)	0.4

[a]Not included individuals with screen-detected colorectal cancer. Advanced adenoma: Adenoma with size 10 mm or lagrer, with villous histology or with high-grade dysplasia.

[b]Of thos who attended the colonoscopy examination.

[c]Perforations (n=6) and admittance to hospital for post-polypectomy bleeding (n=4).

FOBT: Fecal occult blood test

Table 3

Colorectal cancer incidence and mortality in the screening and control group.

	Screening group		Control group		Hazard ratio (95% CI)	p-value
	n	Cases/100,000 py	n	Cases/100,000 py		
Colorectal cancer incidence	253	112.6	1086	141.0.	0.80 (0.70–0.92)	0.001
Person-years of observation		221,429		828,207		
Location						
Distal	137	60.9	621	80.1	0.76 (0.63–0.92)	0.004
Proximal	112	49.8	424	55.5	0.90 (0.73–1.10)	0.3
Sex						
Men	128	115.6	586	157.6	0.73 (0.60–0.89)	0.002
Women	125	109.6	500	125.5	0.87 (0.72–1.06)	0.2
Age group						
50–54 years	40	57.2	315	84.3	0.68 (0.49–0.94)	0.02
55–64 years	213	140.6	771	169.6	0.83 (0.71–0.96)	0.02
Screening modality						
Flexible sigmoidoscopy	114	101.9	1086	141.0	0.72 (0.59–0.87)	0.001
Flexible sigmoidoscopy + FOBT	139	123.3			0.88 (0.74–1.05)	0.2
Colorectal cancer mortality	71	31.4	330	43.1	0.73 (0.56–0.94)	0.02
Person-years of observation		222,677		832,003		
Location						
Distal	39	17.2	168	21.8	0.79 (0.55–1.11)	0.2
Proximal	30	13.4	139	18.3	0.73 (0.49–1.09)	0.1
Sex						
Men	32	28.6	182	49.1	0.58 (0.40–0.85)	0.005
Women	39	34.2	148	37.4	0.91 (0.64–1.30)	0.6
Age group						
50–54 years	12	17.1	87	23.2	0.74 (0.40–1.35)	0.3
55–64 years	59	38.7	243	53.1	0.73 (0.55–0.97)	0.03
Screening modality						
Flexible sigmoidoscopy	41	36.4	330	43.1	0.84 (0.61–1.17)	0.3

	Screening group		Control group		Hazard ratio (95% CI)	p-value
	n	Cases/100,000 py	n	Cases/100,000 py		
Flexible sigmoidoscopy + FOBT	30	26.5			0.62 (0.42–0.90)	0.01
All-cause mortality	2,183	969.0	7,762	994.6	0.97 (0.93–1.02)	0.3

py: person-years of observation

FOBT: Fecal occult blood test.

Table 4

Colorectal cancer stages

Number of localized and advanced colorectal cancers (age-standardized per 1,000 individuals) by randomization group status and by mode of detection.

Stage	Screening group				Control group
	Compliers n=12,955		Noncompliers n=7,617	Total n=20,572	n=78,220
	Screen detected	Post-screen detected			
Localized	29 (2.2)	48 (3.6)	40 (5.4)	117 (5.7)	470 (6.7)
Advanced	10 (0.8)	49 (3.7)	62 (8.3)	120 (5.8)	562 (7.8)
Unclassified	2 (0.1)	4 (0.3)	9 (1.2)	16 (0.8)	54 (0.8)
Total	41 (3.1)	101 (7.6)	111 (15.0)	253 (12.3)	1,086 (15.3)