Annals of Internal Medicine ORIGINAL RESEARCH

Long-Term Effectiveness of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality in Women and Men

A Randomized Trial

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Background: The long-term effects of sigmoidoscopy screening on colorectal cancer (CRC) incidence and mortality in women and men are unclear.

Objective: To determine the effectiveness of flexible sigmoidoscopy screening after 15 years of follow-up in women and men.

Design: Randomized controlled trial. (ClinicalTrials.gov: NCT00119912)

Setting: Oslo and Telemark County, Norway.

Participants: Adults aged 50 to 64 years at baseline without prior CRC.

Intervention: Screening (between 1999 and 2001) with flexible sigmoidoscopy with and without additional fecal blood testing versus no screening. Participants with positive screening results were offered colonoscopy.

Measurements: Age-adjusted CRC incidence and mortality stratified by sex.

Results: Of 98 678 persons, 20 552 were randomly assigned to screening and 78 126 to no screening. Adherence rates were 64.7% in women and 61.4% in men. Median follow-up was 14.8 years. The absolute risks for CRC in women were 1.86% in the screening group and 2.05% in the control group (risk difference, −0.19 percentage point [95% CI, −0.49 to 0.11 percentage point]; HR, 0.92 [CI, 0.79 to 1.07]). In men, the corresponding risks were 1.72% and 2.50%, respectively (risk difference, −0.78 percentage point [CI, −1.08 to −0.48 percentage points]; hazard ratio [HR], 0.66 [CI, 0.57 to 0.78]) (*P* for heterogeneity = 0.004). The absolute risks for death of CRC in women were 0.60% in the screening group and 0.59% in the control group (risk difference, 0.01 percentage point [CI, −0.16 to 0.18 percentage point]; HR, 1.01 [CI, 0.77 to 1.33]). The corresponding risks for death of CRC in men were 0.49% and 0.81%, respectively (risk difference, −0.33 percentage point [CI, −0.49 to −0.16 percentage point]; HR, 0.63 [CI, 0.47 to 0.83]) (*P* for heterogeneity = 0.014).

Limitation: Follow-up through national registries.

Conclusion: Offering sigmoidoscopy screening in Norway reduced CRC incidence and mortality in men but had little or no effect in women.

Primary Funding Source: Norwegian government and Norwegian Cancer Society.

Ann Intern Med. doi:10.7326/M17-1441 **Annals.org**

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This article was published at Annals.org on 24 April 2018.

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† For members of the NORCCAP Study Group, see the **Appendix** (available at Annals.org).

The U.S. Preventive Services Task Force recommends several screening tests for colorectal cancer (CRC) in women and men aged 50 to 75 years, including sigmoidoscopy and the combination of sigmoidoscopy and immunochemical fecal occult blood testing (FOBT) (1). Sigmoidoscopy screening for CRC has been introduced in the United Kingdom and other countries, including Norway. Previous analyses of 4 randomized trials have indicated that sigmoidoscopy screening reduces CRC incidence by 18% to 26% and CRC mortality by 22% to 31% after 10 to 17 years of follow-up (2–5). Evaluating the duration of this effect is important because it may enable guideline makers to recommend evidence-based screening intervals, thus reducing health care costs, patient inconvenience, and adverse events related to screening.

The effectiveness of sigmoidoscopy screening in women is still uncertain. In 3 of the trials, absolute reductions in CRC incidence were larger among men (0.40% to 1.05%) than women (0.13% to 0.42%), whereas 1 trial with shorter follow-up found the opposite (0.38% in women vs. 0.26% in men). Reduction of CRC mortality was consistently larger in men (0.15% to 0.36%) than women (0.04% to 0.17%) (2–6) (Senore C. Personal communication.). Longer follow-up is needed to confirm data on the effectiveness of sigmoidoscopy screening in women and men.

Here, we report data on CRC incidence and mortality after up to 17 years of follow-up in 98 678 women and men. The data are based on NORCCAP (Norwegian Colorectal Cancer Prevention), a population-based, randomized trial of sigmoidoscopy screening with and without additional immunochemical FOBT versus no screening.

See also:

Editorial comment 1
Summary for Patients 2

Web-Only
Supplement

Table. Age-Adjusted Hazard Ratios and Rate Differences for CRC Incidence and Mortality in the Screening Versus Control Group in Women and Men

Variable	Women					
	Screening Group (n = 10 297)		Control Group (n = 39 254)			
	Cases, n	Cases per 100 000 Person-Years, n	Cases, n	Cases per 100 000 Person-Years, n*	Hazard Ratio (95% CI)	Rate Difference per 100 000 Person-Years (95% CI)
CRC incidence	207	140.1	789	153.6	0.92 (0.79 to 1.07)	−13.5 (−35.4 to 8.5)
Person-years of observation		147 762		556 457	–	–
Location†						
Distal	89	60.2	389	74.3	0.81 (0.64 to 1.02)	−14.1 (−28.9 to 1.10)
Proximal	113	76.5	383	76.1	1.01 (0.82 to 1.25)	0.35 (−15.7 to 16.4)
Age group						
50–54 y	39	81.0	237	94.2	0.86 (0.61 to 1.21)	−13.2 (−41.3 to 14.9)
55–64 y	168	168.7	552	181.1	0.93 (0.78 to 1.11)	−12.4 (−42.1 to 17.2)
Screening method						
Sigmoidoscopy	104	140.6	789	153.6	0.92 (0.75 to 1.13)	−12.9 (−41.2 to 17.0)
Sigmoidoscopy + FOBT	103	139.5	789	153.6	0.91 (0.74 to 1.11)	−14.0 (−42.7 to 15.8)
CRC mortality	65	43.7	225	43.3	1.01 (0.77 to 1.33)	0.43 (−11.7 to 12.6)
Person-years of observation		148 705		575 166	–	–
Location†						
Distal	33	22.2	99	18.8	1.17 (0.79 to 1.73)	3.36 (−4.9 to 12.0)
Proximal	27	18.2	114	22.2	0.83 (0.54 to 1.26)	−4.0 (−12.0 to 4.0)
Age group						
50–54 y	12	24.8	70	27.7	0.90 (0.49 to 1.65)	−2.86 (−18.3 to 12.6)
55–64 y	53	52.8	155	50.5	1.05 (0.77 to 1.42)	2.3 (−14.0 to 18.6)
Screening method						
Sigmoidoscopy	35	47.1	225	43.3	1.09 (0.76 to 1.56)	3.78 (−12.9 to 20.5)
Sigmoidoscopy + FOBT	30	40.4	225	43.3	0.94 (0.64 to 1.37)	−2.93 (−17.9 to 13.2)
All-cause mortality	1571	1056.4	5427	1047.5	1.02 (0.96 to 1.07)	8.92 (−49.3 to 66.6)
Age group						
50–54 y	315	652.4	1651	654.0	1.00 (0.88 to 1.13)	−1.5 (−80.2 to 77.1)
55–64 y	1256	1251.4	3776	1230.0	1.02 (0.95 to 1.08)	21.4 (−58.2 to 101.0)

CRC = colorectal cancer; FOBT = fecal occult blood testing.
* Rates are age-standardized.
† The sum of cases of distal and proximal CRC is lower than the total values because the location of some cases of cancer was unknown.

METHODS

Patients and Design

The study design is described elsewhere (7) and in the Supplement (available at Annals.org). In brief, between 1999 and 2000, all women and men aged 55 to 64 years in the city of Oslo and Telemark County, Norway, were identified through the National Registry and randomly assigned to once-only sigmoidoscopy screening or no screening (Section 1 of the Supplement). Persons in the screening group were further randomly assigned (1:1) to receive sigmoidoscopy alone or with a single round of immunochemical FOBT (FlexSure OBT [Beckman Coulter]) (7). Both randomization procedures were done by an independent body (IBM Norway) using computerized algorithms. At the end of 2000, investigators decided to also include all persons aged 50 to 54 years living in the trial areas, as described previously (6) and in Section 1 of the Supplement. Screening was done in 1999 and 2000 for persons aged 55 to 64 years and in 2001 for those aged 50 to 54 years. The only exclusion criterion was history of CRC. During the study, no organized CRC screening and very little opportunistic screening took place in the trial areas (3). 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 Protection Authority. The trial is registered at ClinicalTrials.gov (NCT00119912).

Screening examinations were done at 3 dedicated centers (7, 8). During sigmoidoscopy, detected polyps were removed or biopsied and examined histopathologically. Participants assigned to sigmoidoscopy and FOBT received the FOBT kit by mail and returned it to the screening center at their sigmoidoscopy appointment. A positive result on a screening test was defined as any polyp of 10 mm or larger (regardless of histology), any adenoma, CRC, or positive findings on FOBT. Participants with positive results were referred for colonoscopy for removal of all detected polyps and diagnosis of cancer. Postpolypectomy surveillance was done according to Norwegian guidelines (5- or 10-year colonoscopy intervals for high-risk adenomas and no surveillance for low-risk adenomas) (9).

End Point Ascertainment

Primary study end points were CRC incidence and mortality. Predefined secondary end points included

Table–Continued

Men						*P* Value for Heterogeneity for Women vs. Men
Screening Group (n = 10 255)		Control Group (n = 38 872)				
Cases, *n*	Cases per 100 000 Person-Years, *n*	Cases, *n*	Cases per 100 000 Person-Years, *n**	Hazard Ratio (95% CI)	Rate Difference per 100 000 Person-Years (95% CI)	
186	131.4	962	196.9	0.66 (0.57 to 0.78)	−65.5 (−80.8 to −36.9)	0.004
	141 510		528 317	–	–	
105	74.2	611	124.3	0.59 (0.48 to 0.73)	−50.1 (−62.0 to −28.6)	0.006
78	55.1	326	67.6	0.81 (0.63 to 1.04)	−12.5 (−24.3 to 3.5)	0.31
38	81.9	317	126	0.65 (0.46 to 0.91)	−44.1 (−73.6 to −14.6)	0.25
148	155.6	645	233.1	0.67 (0.56 to 0.80)	−77.5 (−108.4 to −46.7)	0.009
85	119.9	962	196.9	0.60 (0.48 to 0.75)	−77.0 (−91.9 to −35.7)	0.002
101	142.9	962	196.9	0.72 (0.59 to 0.89)	−54.0 (−72.0 to −10.7)	0.27
57	40	305	63.3	0.63 (0.47 to 0.83)	−23.2 (−32.8 to −8.7)	0.014
	142 370		539 415	–	–	
35	24.6	180	37.3	0.65 (0.45 to 0.93)	−12.8 (−20.7 to −1.9)	0.023
20	14.1	112	23.3	0.60 (0.37 to 0.96)	−9.2 (−15.5 to −1.1)	0.43
8	17.2	88	34.8	0.49 (0.24 to 1.02)	−17.6 (−31.6 to −3.7)	0.21
49	51.1	217	77.7	0.66 (0.48 to 0.90)	−26.6 (−44.2 to −8.9)	0.038
29	40.7	305	63.3	0.64 (0.43 to 0.93)	−22.6 (−34.6 to −1.9)	0.010
28	39.3	305	63.3	0.62 (0.42 to 0.91)	−23.9 (−35.3 to −3.3)	0.084
2238	1572.0	8006	1638.1	0.96 (0.91 to 1.00)	−66.1 (−137.5 to 5.77)	0.111
463	995.3	2528	1001.8	0.99 (0.90 to 1.10)	−6.5 (−105.2 to 92.2)	0.96
1775	1853.0	5478	1964.0	0.94 (0.89 to 1.00)	−111.0 (−211.7 to −10.3)	0.076

CRC incidence and mortality in women and men and in the distal colon (defined as rectum and sigmoid colon) and proximal colon. All end points were assessed by linkage of participants' national identity numbers to Norwegian registries (Cancer Registry, Cause of Death Registry, and National Registry) (7). We defined CRC as adenocarcinoma of the colon or rectum.

Statistical Analysis

All primary analyses followed the intention-to-treat principle–that is, participants were classified into their allocated group (screening or control) regardless of adherence to the intervention. All participants were followed from study entry until CRC diagnosis, death, emigration, or 31 December 2015, whichever occurred first. The number of persons eligible for analyses was updated from previous publications for current registry status for those who had emigrated or died before the study started. Details of the sample size calculations have been published previously (3, 7) and are available in Section 2.1 of the Supplement.

We computed rates and 15-year cumulative probabilities (risks) of CRC incidence and mortality, as well as rate differences and 15-year risk differences. All estimates were adjusted for age, as explained in Section 2.2 of the Supplement and elsewhere (3); 95% CIs for the differences were calculated via a nonparametric bootstrap with 10 000 samples. We estimated hazard ratios (HRs) from Cox models (Section 2.2 of the Supplement).

Stratification by sex was a predefined subgroup analysis in the NORCCAP trial. We tested for effect heterogeneity by sex on the additive scale using bootstrapping (7). Because substantial heterogeneity existed between women and men for both CRC incidence (P = 0.004) and mortality (P = 0.014), the steering committee decided to present results for women and men separately. Results for women and men combined are in Section 3 of the Supplement. As secondary analyses, we estimated the per protocol effect among participants who adhered to screening via instrumental variable estimation (Section 2.3 of the Supplement).

All analyses were done with Stata, version 14.1 (StataCorp).

Role of the Funding Source

The study was funded by grants from the Norwegian government and the Norwegian Cancer Society. The funders had no role in the design, conduct, or reporting of the trial.

RESULTS

Of 100 210 randomly assigned persons, 1532 (1.5%) were excluded (because of CRC, death, emigration before study entry, or not being traceable through the National Registry), leaving 98 678 persons eligible for analyses, 20 552 in the screening group and 78 126 in the control group (**Appendix Figure**, available at Annals.org). In the screening group, 10 271 participants were randomly assigned to sigmoidoscopy screening and 10 281 to the combination of sigmoidoscopy and FOBT. Men accounted for 49.8% of the study population.

The screening adherence rates were 64.7% in women and 61.4% in men. Colonoscopy for positive screening results was done in 2520 screened participants (19.5%), 16.2% of women and 22.9% of men. Surveillance was recommended to 493 women (7.4%) and 775 men (12.3%). Adherence to colonoscopy after positive results on sigmoidoscopy or FOBT was high (96%) in both women and men. The median follow-up was 14.8 years for both incidence and mortality.

CRC Incidence in Women

During 704 219 person-years of observation in women, 207 cases of CRC were diagnosed in the screening group and 789 in the control group (**Table**). The incidence rates per 100 000 person-years were 140.1 cases in the screening group and 153.6 in the control group, corresponding to 13.5 fewer cases (95% CI, −35.4 to 8.5 cases) per 100 000 person-years in the screening group and an HR of 0.92 (CI, 0.79 to 1.07) (**Table** and **Figure 1**). The 15-year risks for CRC were 1.86% in the screening group and 2.05% in the control group (risk difference, −0.19 percentage point [CI, −0.49 to 0.11 percentage point]) (**Figure 2**). The CRC incidence rates differed little between the screening and control groups with tumor location (distal vs. proximal colon) or screening method (sigmoidoscopy alone vs. with FOBT).

CRC Incidence in Men

During 669 827 person-years of observation in men, 186 cases of CRC were diagnosed in the screening group and 962 in the control group. The incidence rates per 100 000 person-years were 131.4 cases in the screening group and 196.9 in the control group, corresponding to 65.5 fewer cases (CI, −80.8 to –36.9 cases) per 100 000 person-years in the screening group and an HR of 0.66 (CI, 0.57 to 0.78) (**Table** and **Figure 1**). The 15-year risks for CRC were 1.72% in the screening group and 2.50% in the control group (risk difference, −0.78 percentage point [CI, −1.08 to −0.48 percentage points]) (**Figure 2**).

The HRs were 0.59 (CI, 0.48 to 0.73) for cancer in the distal colon and 0.81 (CI, 0.63 to 1.04) for cancer in the proximal colon (**Table**). The incidence rate was lower in the screening group than in the control group for both older and younger age groups and for sigmoidoscopy with and without FOBT.

CRC Mortality in Women

A total of 290 women died of CRC during follow-up (723 871 person-years of observation), 65 in the screening group and 225 in the control group. The CRC mortality rates per 100 000 person-years were 43.7 deaths in the screening group and 43.3 in the control group, corresponding to 0.4 more deaths (CI, −11.7 to 12.6 deaths) per 100 000 person-years in the screening group and an HR of 1.01 (CI, 0.77 to 1.33) (**Table** and **Figure 1**). The 15-year risks for CRC death were 0.60% in the screening group and 0.59% in the control group (risk difference, 0.01 percentage point [CI, −0.16 to 0.18 percentage point]) (**Figure 2**). The CRC mortality rates differed little with tumor location (distal vs. proximal colon) or screening method (sigmoidoscopy alone vs. with FOBT).

CRC Mortality in Men

A total of 362 men died of CRC during follow-up (681 785 person-years of observation), 57 in the screening group and 305 in the control group. The CRC mortality rates per 100 000 person-years were 40.0 deaths in the screening group and 63.3 in the control group, corresponding to 23.2 fewer deaths (CI, −32.8 to −8.7 deaths) per 100 000 person-years in the screening group and an HR of 0.63 (CI, 0.47 to 0.83) (**Table** and **Figure 1**). The 15-year risks for CRC death were 0.49% in the screening group and 0.81% in the control group (risk difference, −0.33 percentage point [CI, −0.49 to −0.16 percentage point]) (**Figure 2**).

The HRs were 0.65 (CI, 0.45 to 0.93) for death from CRC of the distal colon and 0.60 (CI, 0.37 to 0.96) for that of the proximal colon (**Table**). For sigmoidoscopy screening alone, the HR was 0.64 (CI, 0.43 to 0.93), compared with 0.62 (CI, 0.42 to 0.91) for sigmoidoscopy with FOBT.

Results for women and men combined are in **Supplement Table 1** (available at Annals.org). **Supplement Figures 1** and **2** (available at Annals.org) show cumulative incidence and mortality for screening attenders, nonattenders, and control participants.

All-Cause Mortality

During follow-up, 17 242 deaths (17.5%) occurred: 6998 women (14.1%) and 10 244 men (20.9%). The all-cause mortality rates in women were 1056.4 and 1047.5 deaths per 100 000 person-years in the screening and control groups, respectively (HR, 1.02 [CI, 0.96 to 1.09]). For men, the all-cause mortality rates were 1572.0 and 1638.1 deaths per 100 000 person-years, respectively (HR, 0.96 [CI, 0.91 to 1.00]).

Per Protocol Analyses

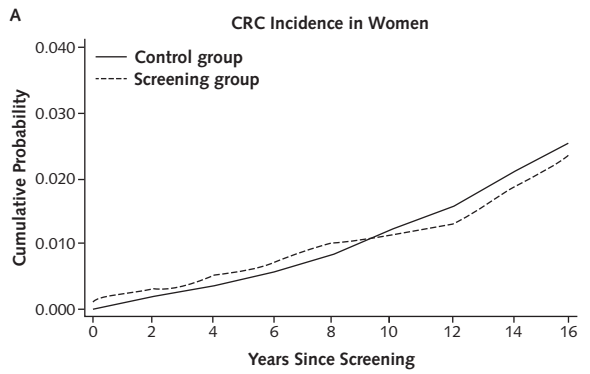
Among participants who adhered to screening, we estimated that the 14-year risk differences for CRC incidence were −0.27 percentage point (CI, −0.72 to 0.18 percentage point) in women and −1.19 percentage points (CI, −1.65 to −0.72 percentage points) in men (**Supplement Table 1**). The estimated 14-year risk

differences for CRC mortality were −0.03 percentage point (CI, −0.27 to 0.21 percentage point) in women and −0.52 percentage point (CI, −0.77 to −0.26 percentage point) in men.

DISCUSSION

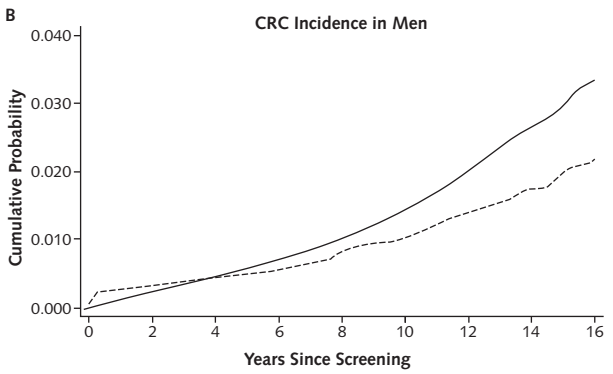
Our findings indicate that once-only sigmoidoscopy screening reduces the risk for CRC incidence over 17 years by 34% in men but does not reduce risk in

Figure 1. Risks for CRC, rectosigmoid cancer, and death of CRC for women and men in the screening and control groups.



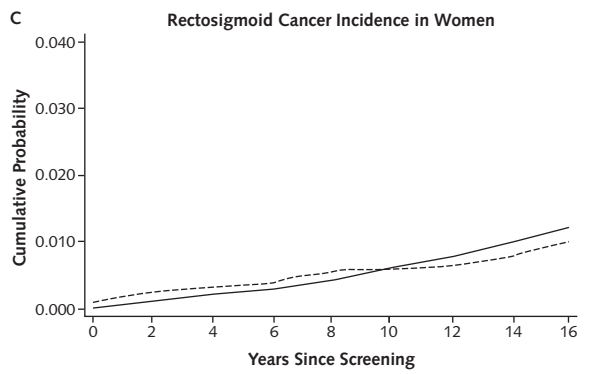
At risk, *n*

Control	39 254	38 575	37 885	37 202	36 419	35 611	34 805	33 788	8472
Screening	10 297	10 112	9942	9765	9559	9371	9149	8860	2665



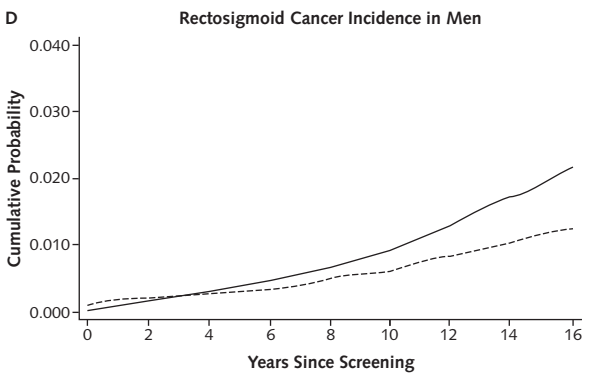
At risk, *n*

Control	38 872	37 897	36 826	35 716	34 630	33 449	32 190	30 841	7128
Screening	10 255	10 006	9745	9479	9172	8852	8510	8172	2363



At risk, *n*

Control	39 254	38 575	37 885	37 202	36 419	35 611	34 805	33 788	8472
Screening	10 297	10 112	9942	9765	9559	9371	9149	8860	2665

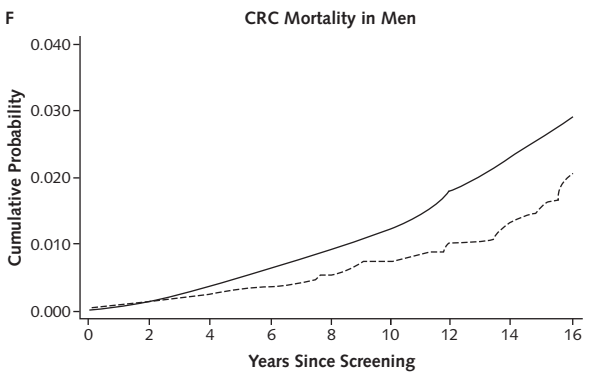


At risk, *n*

Control	38 872	37 897	36 826	35 716	34 630	33 449	32 190	30 841	7128
Screening	10 255	10 006	9745	9479	9172	8852	8510	8172	2363

At risk, *n*

Control	39 254	38 629	37 978	37 336	36 625	35 893	35 144	34 226	8646
Screening	10 297	10 140	9981	9815	9623	9439	9227	8963	2706

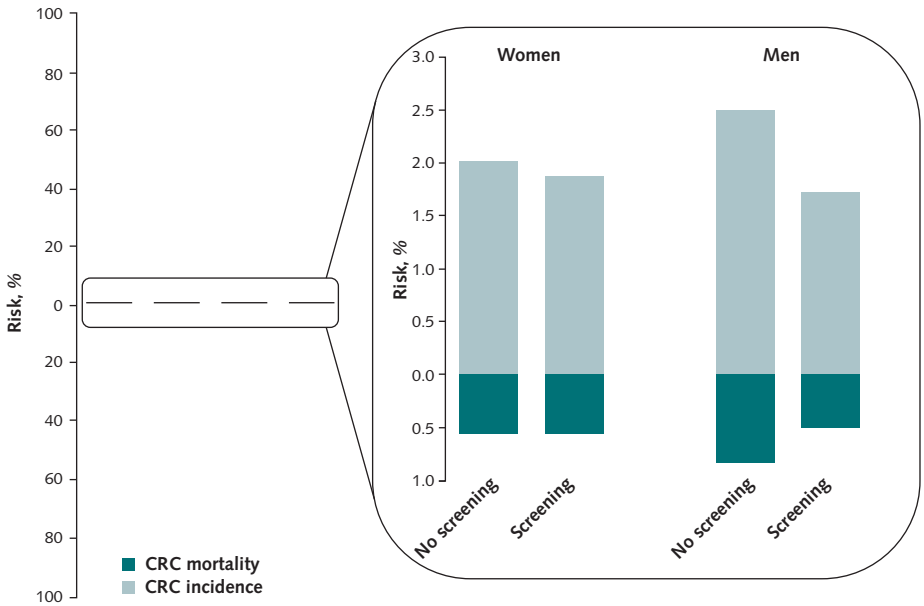


At risk, *n*

Control	38 872	37 960	36 924	35 860	34 838	33 747	32 574	31 338	7289
Screening	10 255	10 030	9777	9518	9225	8912	8590	8266	2396

CRC = colorectal cancer.

Figure 2. Fifteen-year risks for CRC and death of CRC with and without screening for women and men.



CRC = colorectal cancer.

women. For CRC mortality, we observed a 37% reduction in men but little or no reduction in women.

We and others have shown that sigmoidoscopy screening lowers CRC incidence and mortality for 10 to 12 years (3–5, 10). The previous reports also indicated that the effect might be smaller in women than men, but differences varied between studies and between the 2 end points (CRC incidence and mortality). This heterogeneity between studies and end points may have been due to short follow-up, which could have prevented researchers from finding differences in effectiveness between women and men. Different thresholds for colonoscopy referral might also have contributed to the heterogeneity between the sex-specific effects because cancer distribution in the large bowel varies with sex and age (6). Another source of heterogeneity is the difference in surveillance recommendations: More intensive surveillance during follow-up might make the screening intervention more effective.

In a recent pooled analysis of 3 of the 4 randomized trials—which shorter follow-up than in the present report—sigmoidoscopy screening reduced the incidence of CRC by 29% in women younger than 60 years and 24% in men. No screening effect was seen in older women (6).

In this update of the NORCCAP study with longer follow-up and more events, we found a strong effect of sigmoidoscopy screening in men but little or no effect in women. Furthermore, the effect in men lasted beyond what we have previously reported, and we found a strong trend toward reduction in all-cause mortality in men screened by sigmoidoscopy. In comparison, the UK Flexible Sigmoidoscopy Screening trial found that once-only sigmoidoscopy screening was effective in both women and men after 17 years of follow-up, although less so in women, which is consistent with our findings (2). In that trial, CRC incidence decreased by 0.42% in women and 1.05% in men and CRC mortality by 0.17% in women and 0.36% in men.

Why sigmoidoscopy screening has limited or no effect in women is unclear. Because CRC is more prevalent in men than women, the CRC incidence and mortality rates were higher in the male than the female control group, whereas men and women had similar incidence and mortality rates in the screening groups (**Supplement Figures 1C** and **2C**). This could indicate that only a certain risk threshold can be reached by screening regardless of sex. Alternatively, these findings may reflect that women who were screened had a different CRC risk profile from men (screening attendance rates in our study were higher for women than men) (**Supplement Figures 1** and **2**). Men also have a higher prevalence of adenomas at sigmoidoscopy screening, and accordingly, men were more often referred for colonoscopy. In NORCCAP, screening reduced both proximal and distal cancer and cancer death in men, but not in women. Finally, the quality of the screening examination and follow-up colonoscopy in persons with positive screening results may have differed by sex: Women had a slightly shorter intubation depth on sigmoidoscopy (44 vs. 49 cm) and lower cecum intubation rate on colonoscopy (87% vs. 93%). However, the quality of bowel preparation was similar for women and men (8). We cannot rule out or confirm any of these possible explanations, although we find them unlikely to explain the observed differences.

Differences in transition rates and sojourn time (screen-detectable period) of preclinical CRC are also

unlikely to explain our finding, because similar estimates have been found in women and men (11). Finally, women have a higher risk than men for proximal colon cancer, which often has a more aggressive course than distal cancer (12). This may affect the effectiveness of sigmoidoscopy screening in women but does not explain the lack of effect of screening also in the distal colon (6).

Our finding that sigmoidoscopy is not effective in women may have implications for future screening programs using sigmoidoscopy, such as those in the United Kingdom, Italy, and Norway. Studies of biennial FOBT screening have also reported a lower effect in women than men (13). Sex-specific guidelines are not available but may be appropriate to consider. Colonoscopy may be a better screening method than sigmoidoscopy in women, as suggested by others (14). However, this is uncertain because randomized trials on the effectiveness of colonoscopy screening are still ongoing (15).

Our study comprised 2 screening groups, sigmoidoscopy alone and sigmoidoscopy with FOBT. We did not find meaningful differences between these 2 methods with regard to CRC incidence or mortality (**Table** and **Supplement Table 1**). Thus, according to our results, adding once-only FOBT to sigmoidoscopy screening does not improve efficiency. Only repeated FOBT has been shown to be effective (16).

We found a possible minor beneficial effect of sigmoidoscopy screening on all-cause mortality in men (HR, 0.96 [CI, 0.91 to 1.00]), which has been confirmed in a recent meta-analysis (17). This important observation may affect screening acceptance. The meta-analyses, however, did not report results for women and men separately.

Current guidelines recommend repeated sigmoidoscopy screening at 5- to 10-year intervals (1). We show that once-only sigmoidoscopy has a sustained effect for a follow-up of 15 years. An extension to 12- or 15-year intervals would result in substantial savings for the health care system and reduce the individual burden of screening, including patient discomfort and risk for adverse events and complications. Sigmoidoscopy is generally well-tolerated but is still invasive. Up to 10% of patients (more commonly women) have moderate or severe pain during the procedure (18–20).

Although NORCCAP is a large, population-based, carefully done intervention trial, it has some limitations. It was originally designed for women and men aged 55 to 64 years. Even though sex-specific analyses were prespecified, we decided to report results separately for women and men only after detecting a positive interaction between sex and randomization group. Still, we believe that presenting the combined results as the main finding would have been misleading given the observed heterogeneity between women and men. We consider a sex-stratified meta-analysis to be highly desirable, but combining data from NORCCAP and the other trials of flexible sigmoidoscopy screening may produce results that are no longer generalizable. Because of its population-based design, NORCCAP evaluates the effectiveness of sigmoidoscopy screening in a population, whereas the other studies (by including volunteers) are efficacy trials. Another limitation is our lack of data on CRC treatment in the study population, but because Norway's health care system provides universal coverage, access to treatment should not differ between the screening and control groups. However, treatment strategies are unlikely to affect incidence, and women and men also differed in CRC incidence. Finally, we did not have information about socioeconomic status or ethnicity in the screening and control groups, but because of NORCCAP's randomized design, these covariates are expected to be equally distributed between the groups.

In conclusion, the effect of sigmoidoscopy screening was long-lasting in men, with absolute risk reductions of 0.78% for CRC incidence (from 2.50% to 1.72%) and 0.33% for CRC mortality (from 0.81% to 0.49%). For women, we could not detect an effect of sigmoidoscopy screening on incidence or mortality. Our results may have implications for future screening recommendations and trial design, where sex-stratified evaluations and sample size calculations should be considered. We further believe that communicating absolute rather than relative risk reductions, as in the present paper (**Figure 2**), would be preferable during shared decision making with patients.

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Disclaimer: Drs. Holme, Løberg, Kalager, and Bretthauer had full access to all data and take responsibility for the integrity of the data and accuracy of the analysis.

Grant Support: By research grants from the Norwegian government and the Norwegian Cancer Society. Work with the present manuscript was funded by research grants from the Norwegian Cancer Society, the Research Council of Norway,

the South-East Regional Health Authority of Norway, the Fulbright Foundation, Sørlandet Hospital Kristiansand, and the National Institutes of Health.

Disclosures: Dr. Holme reports personal fees from Norgine outside the submitted work. Dr. Hernán reports grants from the National Institutes of Health during the conduct of the study. Dr. Hoff reports personal fees from Amgen Norway during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-1441.

Reproducible Research Statement: *Study protocol:* See the Supplement (available at Annals.org). *Statistical code:* Available from Dr. Løberg (e-mail, magnus.loberg@medisin.uio.no). *Data set:* May be available after written agreement with the NORCCAP steering committee (e-mail, geir.hoff@kreftregisteret.no).

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References

1. **Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, et al; US Preventive Services Task Force.** Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:2564-75. [PMID: 27304597] doi:10.1001/jama.2016.5989

2. **Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, et al.** Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet. 2017;389:1299-1311. [PMID: 28236467] doi:10.1016/S0140-6736(17)30396-3

3. **Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, et al.** Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. 2014;312:606-15. [PMID: 25117129] doi:10.1001/jama.2014.8266

4. **Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al; PLCO Project Team.** Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366:2345-57. [PMID: 22612596] doi:10.1056/NEJMoa1114635

5. **Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al; SCORE Working Group.** Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial–SCORE. J Natl Cancer Inst. 2011;103:1310-22. [PMID: 21852264] doi:10.1093/jnci/djr284

6. **Holme Ø, Schoen RE, Senore C, Segnan N, Hoff G, Løberg M, et al.** Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. BMJ. 2017;356:i6673. [PMID: 28087510] doi:10.1136/bmj.i6673

7. **Bretthauer M, Gondal G, Larsen K, Carlsen E, Eide TJ, Grotmol T, et al.** Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). Scand J Gastroenterol. 2002;37:568-73. [PMID: 12059059]

8. **Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G.** The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scand J Gastroenterol. 2003;38:635-42. [PMID: 12825872]

9. **Hoff G, Sauar J, Hofstad B, Vatn MH.** The Norwegian guidelines for surveillance after polypectomy: 10-year intervals. Scand J Gastroenterol. 1996;31:834-6. [PMID: 8888428]

10. **Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al; UK Flexible Sigmoidoscopy Trial Investigators.** Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624-33. [PMID: 20430429] doi:10.1016/S0140-6736(10)60551-X

11. **Brenner H, Altenhofen L, Katalinic A, Lansdorp-Vogelaar I, Hoffmeister M.** Sojourn time of preclinical colorectal cancer by sex and age: estimates from the German national screening colonoscopy database. Am J Epidemiol. 2011;174:1140-6. [PMID: 21984657] doi:10.1093/aje/kwr188

12. **Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK.** Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21:5167-75. [PMID: 25954090] doi:10.3748/wjg.v21.i17.5167

13. **Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, et al.** Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369:1106-14. [PMID: 24047060] doi:10.1056/NEJMoa1300720

14. **Schoenfeld P, Cash B, Flood A, Dobhan R, Eastone J, Coyle W, et al; CONCeRN Study Investigators.** Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med. 2005;352:2061-8. [PMID: 15901859]

15. **Robertson DJ, Kaminski MF, Bretthauer M.** Effectiveness, training and quality assurance of colonoscopy screening for colorectal cancer. Gut. 2015;64:982-90. [PMID: 25804631] doi:10.1136/gutjnl-2014-308076

16. **Hewitson P, Glasziou P, Irwig L, Towler B, Watson E.** Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007:CD001216. [PMID: 17253456]

17. **Swartz AW, Eberth JM, Josey MJ, Strayer SM.** Reanalysis of all-cause mortality in the U.S. Preventive Services Task Force 2016 evidence report on colorectal cancer screening. Ann Intern Med. 2017;167:602-3. [PMID: 28828493] doi:10.7326/M17-0859

18. **Robb KA, Lo SH, Power E, Kralj-Hans I, Edwards R, Vance M, et al.** Patient-reported outcomes following flexible sigmoidoscopy screening for colorectal cancer in a demonstration screening programme in the UK. J Med Screen. 2012;19:171-6. [PMID: 23486697] doi:10.1258/jms.2012.012129

19. **Larsen IK, Grotmol T, Bretthauer M, Gondal G, Huppertz-Hauss G, Hofstad B, et al.** Continuous evaluation of patient satisfaction in endoscopy centres. Scand J Gastroenterol. 2002;37:850-5. [PMID: 12190102]

20. **Senore C, Ederle A, Fantin A, Andreoni B, Bisanti L, Grazzini G, et al.** Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. J Med Screen. 2011;18:128-34. [PMID: 22045821] doi:10.1258/jms.2011.010135

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Appendix: NORCCAP Study Group

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Dedicated nurses and staff at the screening centers made this trial possible.

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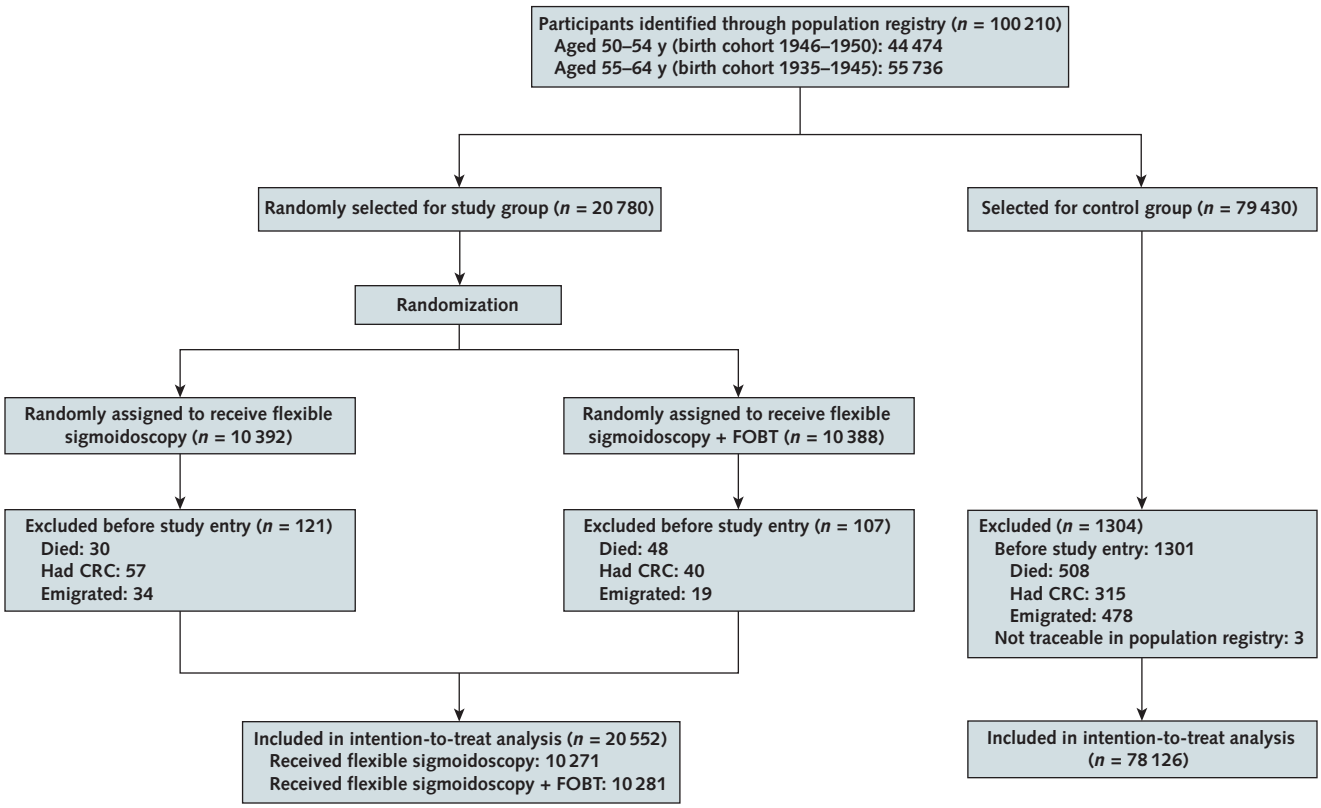
Appendix Figure. Study flow chart.



CRC = colorectal cancer; FOBT = fecal occult blood testing.