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15-Year Benefits of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality

A Pooled Analysis of Randomized Trials

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Background: The effectiveness of screening for colorectal cancer (CRC) by sex and age in randomized trials is uncertain.

Objective: To evaluate the 15-year effect of sigmoidoscopy screening on CRC incidence and mortality.

Design: Pooled analysis of 4 large-scale randomized trials of sigmoidoscopy screening.

Setting: Norway, the United States, the United Kingdom, and Italy.

Participants: Women and men aged 55 to 64 years at enrollment.

Intervention: Sigmoidoscopy screening.

Measurements: Primary end points were cumulative incidence rate ratio (IRR) and mortality rate ratio (MRR) and rate differences after 15 years of follow-up comparing screening versus usual care in intention-to-treat analyses. Stratified analyses were done by sex, cancer site, and age at screening.

Results: Analyses comprised 274 952 persons (50.7% women), 137 493 in the screening and 137 459 in the usual care group. Screening attendance was 58% to 84%. After 15 years, the rate difference for CRC incidence was 0.51 cases (95% CI, 0.40 to 0.63 cases) per 100 persons and the IRR was 0.79 (CI, 0.75 to 0.83). The rate difference for CRC mortality was 0.13 deaths (CI, 0.07 to 0.19 deaths) per 100 persons, and the MRR was 0.80 (CI, 0.72 to 0.88). Women had less benefit from screening than men for CRC incidence (IRR for women, 0.84 [CI, 0.77 to 0.91]; IRR for men, 0.75 [CI, 0.70 to 0.81]; $P = 0.032$ for difference) and mortality (MRR for women, 0.91 [CI, 0.77 to 1.17]; MRR for men, 0.73 [CI, 0.64 to 0.83]; $P = 0.025$ for difference). There was no statistically significant difference in screening effect between persons aged 55 to 59 years and those aged 60 to 64 years.

Limitation: Data from the U.K. trial were less granular because of privacy regulations.

Conclusion: This pooled analysis of all large randomized trials of sigmoidoscopy screening demonstrates a significant and sustained effect of sigmoidoscopy on CRC incidence and mortality for 15 years.

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With more than 1.9 million new cases and more than 930 000 deaths each year, colorectal cancer (CRC) is the third most common cancer worldwide (1). Endoscopic screening with sigmoidoscopy or colonoscopy in average-risk populations provides the largest potential for reduction of CRC incidence and mortality by detection and removal of premalignant polyps and detection of early cancer (2). However, precise quantification of the long-term benefits and harms of endoscopic screening has been difficult because of the lack of pooled analyses of randomized trials with long-term follow-up (2, 3).

We have undertaken a meta-analysis of randomized trials of endoscopic screening for CRC (4). The analyses included 3 trials of sigmoidoscopy screening from Norway, the United States, and Italy comprising 288 000 participants in total and with follow-up for 10 to 12 years. The results suggested less benefit of sigmoidoscopy screening in terms of CRC incidence and mortality in older women (3, 4). Our analysis was done before recent updates from the U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening) (5) and Italian SCORE (Screening for Colon Rectum) (6) trials and did not include UKFSST (UK Flexible Sigmoidoscopy Screening Trial), which comprises 37% of all persons included in randomized trials of sigmoidoscopy screening worldwide (5–8).

The aim of the current study was to update and extend our previous analyses by including the most recent data of all 4 randomized trials of sigmoidoscopy screening with long-term follow-up to quantify screening effectiveness in terms of CRC incidence and mortality. We also provide new evidence-based quantification of screening benefits for women and men in various age groups to inform screening guidelines and enable shared decision making.

Methods

The current work is a collaborative project of investigators from the 4 randomized controlled trials on average-

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risk population screening with sigmoidoscopy; these trials are from Norway (NORCCAP [Norwegian Colorectal Cancer Prevention]) (7), the United States (PLCO) (5), the United Kingdom (UKFSST) (8), and Italy (SCORE) (6). Details on each trial have been published previously (5–8) and are described in Supplement Part 1 (available at Annals.org). The trials were run by academic or governmental investigators and sponsored by research grants in their respective countries. All trials were approved by ethics committees in their countries or regions and are registered in clinical trial registries.

Table 1 shows the number of persons aged 55 to 64 years invited to screening, screening timelines, and attendance and follow-up in the 4 trials. The trials in Norway, the United Kingdom, and Italy applied once-only sigmoidoscopy screening, whereas the U.S. trial offered a second screening sigmoidoscopy 3 or 5 years after the first. Either polyps were removed at sigmoidoscopy or the patient was referred for colonoscopy or for surgery if indicated. Colonoscopy referral depended on polyp characteristics, and the definition of a positive screening result differed across trials (Table 1). Primary end points in all trials were the comparison of sigmoidoscopy screening versus usual care on CRC incidence and mortality by intention-to-treat analyses after 15 years.

The trials in the United States, the United Kingdom, and Italy had a design based on solicitation of expression of interest before randomization. The Norwegian trial had a preconsent randomization directly from the population registry. All trials obtained consent from those who attended screening.

Primary and Secondary Outcomes

Predefined primary outcomes were CRC incidence and mortality after sigmoidoscopy screening compared with usual care after 15 years of follow-up in intention-to-treat analyses of average-risk persons aged 55 to 64 years at enrollment. Only participants aged 55 to 64 years at enrollment were selected for analyses because these age groups were included in all 4 trials.

Secondary outcomes were CRC incidence and mortality by cancer site (distal vs. proximal colon), sex, and 5-year age group (55 to 59 years vs. 60 to 64 years at enrollment) and all-cause mortality. The distal colon included the rectum, sigmoid, and descending colon, whereas the proximal colon included the splenic flexure, transverse colon, hepatic flexure, ascending colon, and cecum, including the appendix.

Data Acquisition

We obtained aggregated anonymized data. From the U.S., Italian, and Norwegian trials, we had yearly data on numbers of persons at risk, CRC cases (including cancer site), and deaths (CRC-specific and all-cause), by randomization group, sex, and 5-year age group. From the U.K. trial, because of the recent introduction of stricter regulations, we had 3-yearly data on numbers of persons at risk, CRC cases (including cancer site), and deaths (CRC-specific and all-cause), by randomization group, sex, and 5-year age group. To obtain yearly data on all trials, we distributed the 3-yearly CRC and death data from the United Kingdom equally over the respective 3 consecutive years, except for the first 3 years in the screening group where we obtained the exact number of screen-detected cancer cases (8) for the first year. The remaining cases (total number of CRC cases in the 3-year period minus screen-detected CRC cases) were evenly distributed in years 1, 2, and 3 (first year was included because screen-detected cancer applies only for those who adhere to screening). Supplement Part 2 (available at Annals.org) provides details on data acquisition.

The cancer site–specific and death data from the U.K. trial were further restricted. When observed events were fewer than 8, data were reported as "0 to 7." We imputed the value of 7, which may overestimate number of events for these analyses. This applies to the screening and usual care groups.

Trial information on CRC deaths per cancer site from the United Kingdom were omitted because some strata had few events. Accordingly, the pooled analyses of CRC mortality by cancer site are without the U.K. data. Data from the PLCO trial differed somewhat from those previously published (5) because some participants had recently withdrawn consent. Data were merged into a database at the University of Oslo, Norway.

From each trial, we extracted information on screening participation, referral rates to colonoscopy after positive sigmoidoscopy results, colonoscopy attendance, cecum intubation rate at colonoscopy, and cancer diagnosed at screening or colonoscopy follow-up per age group at enrollment (55 to 59 years or 60 to 64 years) (5–8). The number of persons referred for colonoscopy and cecum intubation rate at colonoscopy were not available from the U.S. and U.K. trials.

Acquisition of CRC incidence and mortality data was according to standardized procedures in each trial and comprised analysis of national or regional registries for cancer and death with dedicated queries for completeness and accuracy, as described in the original reports (5–8).

Statistical Analysis

We did pairwise comparisons for the pooled screening versus usual care groups at 15 years of follow-up, which was the minimum participant follow-up time across the 4 trials. Because of different risk for CRC in each country and different randomization ratios between screening and usual care groups (Norway, 1:3; United States, 1:1; United Kingdom, 1:2; and Italy, 1:1), we reduced the size of the usual care group by division (that is, reducing numbers for participants, CRC cases, and deaths) in NORCCAP and UKFSST to have a 1:1 ratio, so that the contribution to the screening and usual care groups from each trial was similar at enrollment in the pooled analyses. Supplement Part 2 provides details on the size reduction of the usual care group and data pooling.

We used a Poisson model to calculate yearly CRC incidence rate ratios (IRRs), CRC mortality rate ratios (MRRs), and all-cause mortality, overall and by sex during the 15-year follow-up period. The results are presented as yearly and cumulative incidence and mortality plots. Cumulative CRC incidence and mortality rates over 15 years were calculated using Kaplan–Meier estimates, overall and stratified by cancer site, sex, and 5-year age group (overall

and by sex), and reported as IRR, MRR, and cumulative rate differences per 100 persons with 95% CIs. The χ^2 test was used for rate ratio differences between subgroups (for example, by trial and women vs. men) in effect on CRC incidence and mortality.

In a sensitivity analysis, we used a meta-analysis approach to test the effect of reducing the usual care group in the Norwegian and U.S. trials. In an intention-to-screen analysis, we used the number of included participants and number of events from each trial and estimated the 15-year risk ratios for CRC incidence and CRC mortality, including 95% CIs, overall and by site and sex. We used a random-effects model.

Other sensitivity analyses included removal of individual trials to explore changes in the pooled results without each trial and inclusion of all age groups enrolled in the trials (by adding those aged 50 to 54 years in NORCCAP and 65 to 74 years in PLCO) in addition to the primary analyses of persons aged 55 to 64 years at enrollment.

All analyses were intention-to-treat analyses that included all randomly assigned participants. Tests were 2-sided, and *P* values less than 0.05 were considered statistically significant. We used Stata 17.0 (StataCorp) for all analyses.

Role of the Funding Source

The study sponsors had no role in the study design; data collection, analysis, or interpretation; writing of the report; or decision to submit the manuscript for publication.

RESULTS

Baseline Characteristics

In total, the 4 trials comprised 358 204 participants aged 55 to 64 years (50.7% women; 49.3% men); 137 493

Table 1. Baseline Characteristics of Included Randomized Sigmoidoscopy Screening Trials*

Characteristic	NORCCAP		PLCO		UKFSST		SCORE		Total
Country	Norway		United States		United Kingdom		Italy		–
Inclusion period	1999–2000		1993–2001		1994–1999		1995–1999		–
Randomization and consent procedure	Preconsent randomization based on national population registry		Expression of interest before randomization		Expression of interest before randomization		Expression of interest before randomization		–
Participants included in analysis, *n*									
Total	27 275		99 208		114 197		34 272		274 952
Women	13 789		50 436		58 223		17 051		139 499
Men	13 486		48 772		55 974		17 221		135 453
55–59 y	14 821		51 660		57 296		19 243		143 020
60–64 y	12 454		47 548		56 901		15 029		131 932
Attendance rate for sigmoidoscopy, %	65†		84		71		58		–
Women	67†		82		69		54		–
Men	63†		86		73		61		–
Definition of positive screening test result	Cancer or adenoma, polyp ≥10 mm detected at baseline sigmoidoscopy, or positive result on fecal occult blood test		Finding of a polyp or mass at baseline sigmoidoscopy		CRC, polyps ≥10 mm, ≥3 adenomas, adenomas <10 mm with tubulovillous or villous histology, or severe dysplasia		CRC, polyps ≥5 mm, ≥3 adenomas, adenomas ≤5 mm with a villous histology of >20%, or severe dysplasia		–
National screening program during trial screening period	No organized CRC screening and very little opportunistic screening		Opportunistic screening		No organized CRC screening and very little opportunistic screening		Opportunistic screening		–
	55-59 y	**60-64 y**	**55-59 y**	**60-64 y**	**55-59 y**	**60-64 y**	**55-59 y**	**60-64 y**	
Baseline findings									
Persons invited to screening, *n*	7373	6265	25 838	23 783	28 561	28 537	9567	7569	137 493
Attended screening, *n (%)*	4773 (64.7)	4073 (65.0)	21 718 (84.1)	20 053 (84.3)	20 437 (71.6)	20 184 (70.7)	5707 (59.7)	4291 (56.7)	101 236 (73.6)
Referred for colonoscopy, *n (%)*	999 (13.5)	959 (15.3)	–	–	962 (3.4)	1165 (4.08)	441 (4.60)	386 (5.09)	4912 (5.6)‡
Attended colonoscopy, *n (%)*	961 (13.0)	913 (14.6)	3447 (13.3)	3693 (15.5)	929 (3.3)	1118 (3.91)	408 (4.26)	362 (4.78)	11 831 (8.6)
Cecum intubation, *n (%)*§	922 (12.5)	847 (13.5)	2954 (11.4)	2910 (12.2)	–	–	302 (3.15)	275 (3.63)	8210 (10.2)‖
Screen-detected CRC cases, *n (%)*¶	17 (0.2)	16 (0.3)	38 (0.1)	65 (0.3)	48 (0.2)	92 (0.3)	34 (0.4)	20 (0.3)	330 (0.2)

CRC = colorectal cancer; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening; SCORE = Screening for Colon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial.

* Half of participants in the NORCCAP trial randomly assigned to the screening group were invited to provide a stool sample for fecal occult blood testing in addition to sigmoidoscopy. Participants in the PLCO trial randomly assigned to the screening group were offered a second sigmoidoscopy after 3 or 5 y. These second sigmoidoscopies are not included in the baseline findings.

† The only study with a pragmatic design (preconsent randomization), thus not comparable to the others.

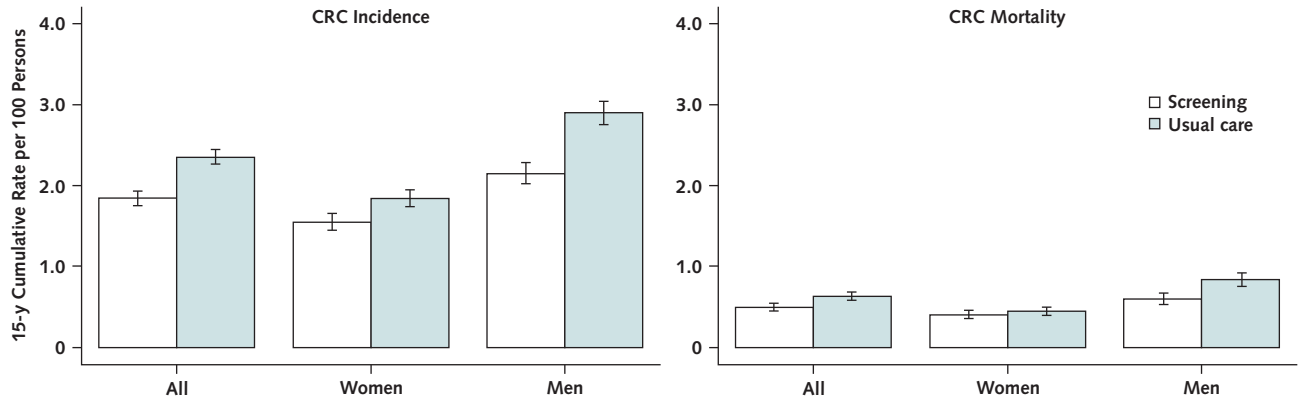
‡ Without PLCO.

§ 97 participants in NORCCAP (55–59 y: 56 persons; 60–64 y: 41 persons) had cecum intubation at initial sigmoidoscopy.

‖ Without UKFSST.

¶ As defined in each trial.

Figure 1. Pooled 15-year cumulative incidence rates (*left*) and cumulative mortality rates (*right*) of CRC per 100 persons after sigmoidoscopy screening for all participants combined and for women and men separately.



Age at enrollment was 55 to 64 y. White bars represent persons randomly assigned to screening, and green bars represent those randomly assigned to usual care. Black whiskers represent 95% CIs. CRC = colorectal cancer.

were randomly assigned to screening and 220 711 to usual care. Using a 1:1 randomization ratio between the screening and usual care groups, our main analysis had 137 493 persons in the screening group and 137 459 in the usual care group (**Tables 1 and 2**). Among participants randomly assigned to screening, screening attendance varied from 58% to 84% in the trials (**Table 1**). The proportion of participants who were referred to and attended colonoscopy among those invited to sigmoidoscopy screening was higher in the Norwegian (13.7%) and U.S. (14.4%) trials and lower in the U.K. (3.6%) and Italian (4.5%) trials (**Table 1**). At screening, CRC detection was highest in the Italian trial at 0.32%, compared with 0.25% in the U.K. trial, 0.24% in the Norwegian trial, and 0.21% in the U.S. trial.

CRC Incidence

Follow-up time for CRC incidence was 3 820 445 person-years. The pooled cumulative incidence of CRC after 15 years of follow-up was 1.84 cases (95% CI, 1.77 to 1.92 cases) per 100 persons in the screening group and 2.35 cases (CI, 2.27 to 2.44 cases) per 100 persons in the usual care group (**Figures 1** and **2**, *top*). This corresponds to a 21% reduction in CRC incidence in the screening group compared with the usual care group (IRR, 0.79 [CI, 0.75 to 0.83]) (**Table 2**). The effect on cumulative CRC incidence was confined to the distal colon (IRR, 0.68 [CI, 0.63 to 0.73]), and there was no evidence of effect in the proximal colon (IRR, 0.94 [CI, 0.87 to 1.03]) (**Table 2**).

In women, the cumulative CRC incidence was 1.55 cases (CI, 1.46 to 1.65 cases) per 100 persons in the screening group and 1.84 cases (CI, 1.74 to 1.95 cases) per 100 persons in the usual care group (**Table 3**; **Supplement Figure**, *A*, available at Annals.org). This corresponds to a 16% reduction in CRC incidence in the screening group compared with the usual care group (IRR, 0.84 [CI, 0.77 to 0.91]). In men, the cumulative CRC incidence was 2.15 cases (CI, 2.03 to 2.27 cases) per 100 persons in the screening group and 2.90 cases (CI, 2.76 to 3.03 cases) per 100 persons in the usual care group. This corresponds to a 25% reduction in CRC incidence in the screening group compared with the usual care group (IRR, 0.75 [CI, 0.70 to 0.81]) (χ^2 test $P = 0.032$ for difference between women and men).

In persons aged 55 to 59 years, the cumulative CRC incidence was 1.51 cases (CI, 1.42 to 1.60 cases) per 100 persons in the screening group and 2.01 cases (CI, 1.90 to 2.12 cases) per 100 persons in the usual care group (IRR, 0.75 [CI, 0.69 to 0.82]). In persons aged 60 to 64 years, the cumulative CRC incidence was 2.21 cases (CI, 2.10 to 2.33 cases) per 100 persons in the screening group and 2.74 cases (CI, 2.61 to 2.87 cases) per 100 persons in the usual care group (IRR, 0.81 [CI, 0.76 to 0.87]). The effect was similar across age groups (χ^2 test $P = 0.169$).

Reductions in CRC incidence in screening compared with usual care were similar for women (IRR, 0.76 [CI, 0.67 to 0.87]) and men (IRR, 0.75 [CI, 0.67 to 0.83]) aged 55 to 59 years (**Table 3**). Among women aged 60 to 64 years, the screening effect attenuated (IRR, 0.91 [CI, 0.81 to 1.01]) (χ^2 test $P = 0.040$), whereas it remained the same for older men (IRR, 0.75 [CI, 0.68 to 0.83]) (χ^2 test $P = 0.93$).

Yearly IRRs are presented in **Figure 3** (*top*), showing consistent screening benefit throughout the entire 15-year follow-up (except for the first year, due to screen-detected lesions and lead time). The pattern was similar for women and men, but the screening benefit was more pronounced in men than women across follow-up.

CRC Mortality

Follow-up time for CRC mortality was 4 242 915 person-years. The pooled cumulative CRC mortality after 15 years of follow-up was 0.51 deaths (CI, 0.48 to 0.56 deaths) per 100 persons in the screening group and 0.65 deaths (CI, 0.61 to 0.70 deaths) per 100 persons in the usual care group (**Figures 1** and **2**, *bottom*). This corresponds to a 20% reduction in CRC mortality in the screening group compared with the usual care group (MRR, 0.80 [CI, 0.72 to 0.88]) (**Table 2**).

The CRC mortality reduction due to screening was confined to the distal colon (MRR, 0.74 [CI, 0.61 to 0.90]) and not observed in the proximal colon (MRR, 0.95 [CI, 0.77 to 1.17]) (Table 2).

In women, the cumulative mortality from CRC was 0.43 deaths (CI, 0.38 to 0.48 deaths) per 100 persons in the screening group and 0.46 deaths (CI, 0.41 to 0.52 deaths) per 100 persons in the usual care group (MRR, 0.91 [CI, 0.77 to 1.07]) (Table 3; Supplement Figure, *B*, available at Annals.org). In men, the cumulative CRC mortality was 0.62 deaths (CI, 0.56 to 0.68 deaths) per 100 persons in the screening group and 0.86 deaths (CI, 0.78 to 0.93 deaths) per 100 persons in the usual care group (MRR, 0.73 [CI, 0.64 to 0.83]). The reduction was smaller in women than men (χ^2 test $P = 0.025$).

Among persons aged 55 to 59 years, the cumulative CRC mortality was 0.41 deaths (CI, 0.37 to 0.46 deaths) per 100 persons in the screening group and 0.54 deaths (CI, 0.49 to 0.60 deaths) per 100 persons in the usual care group (MRR, 0.77 [CI, 0.65 to 0.90]). Among persons aged 60 to 64 years, the cumulative CRC incidence was 0.63 cases (CI, 0.57 to 0.70 cases) per 100 persons in the screening group and 0.78 cases (CI, 0.71 to 0.85 cases) per 100 persons in the usual care group (MRR, 0.81 [CI, 0.71 to 0.94]). The results were similar across age groups (χ^2 test $P = 0.60$).

The screening benefit in terms of CRC mortality was larger among younger women (MRR for ages 55 to 59 years, 0.82 [CI, 0.64 to 1.07]) than older women (MRR for ages 60 to 64 years, 0.99 [CI, 0.79 to 1.23]), but the difference was not statistically significant (χ^2 test $P = 0.26$). In men, the MRRs were similar in the 2 age groups (MRR for ages 55 to 59 years, 0.72 [CI, 0.59 to 0.89]; MRR for ages 60 to 64 years, 0.72 [CI, 0.60 to 0.86]) (χ^2 test $P = 0.83$).

Yearly MRR estimates were below 1 throughout the first 13 years of follow-up (Figure 3, *bottom*) and most pronounced in years 10 to 12 of follow-up. Throughout the follow-up period, women and men had similar MRR patterns, but the yearly estimates were closer to or above 1 in women in follow-up years 5 to 9 (Figure 3, *bottom*).

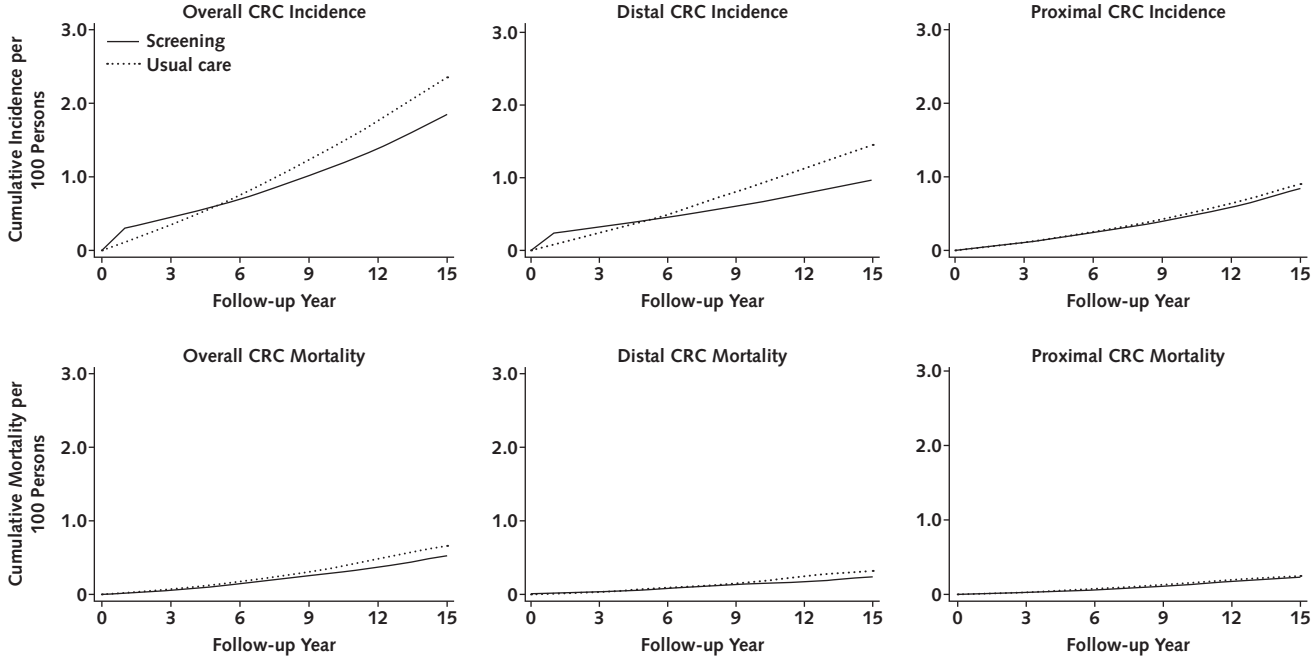
All-Cause Mortality

Follow-up time for all-cause mortality was 4 242 915 person-years. The pooled cumulative all-cause mortality after 15 years of follow-up was 14.3 deaths (CI, 14.1 to 14.5 deaths) per 100 persons in the screening group and 14.6 deaths (CI, 14.4 to 14.8 deaths) per 100 persons in the usual care group. This corresponds to a 2% reduction in all-cause mortality with screening compared with usual care (MRR, 0.98 [CI, 0.95 to 1.00]; $P = 0.016$); this reduction was 2% for women (MRR, 0.98 [CI, 0.96 to 1.01]; $P = 0.24$) and 3% for men (MRR, 0.97 [CI, 0.94 to 1.00]; $P = 0.029$).

Sensitivity Analysis

The results using the meta-analysis approach were similar to those in the pooled analysis (Supplement Table 1, available at Annals.org). The results for CRC

Figure 2. Pooled cumulative CRC incidence (*top*) and mortality (*bottom*) per 100 persons, comparing sigmoidoscopy screening with usual care in intention-to-treat analyses.



Age at enrollment was 55 to 64 y. Solid lines represent persons randomly assigned to screening, and dotted lines represent those randomly assigned to usual care. Distal and proximal CRC mortality plots are without data from the UKFSST (UK Flexible Sigmoidoscopy Screening Trial). CRC = colorectal cancer.

Table 2. Pooled Analysis of CRC Incidence and Mortality in Randomized Sigmoidoscopy Screening Trials*

Variable	Screening, *n*		Usual Care, *n*		Intention-to-Screen Analysis (95% CI)†	
	Cases	Participants	Cases	Participants	Rate Ratio	Rate Difference‡
CRC incidence						
Trial						
NORCCAP	291	13 638	366	13 637	0.79 (0.67 to 0.92)	0.66 (0.24 to 1.08)
PLCO	668	49 621	812	49 587	0.82 (0.74 to 0.90)	0.32 (0.17 to 0.47)
UKFSST	1034	57 098	1361	57 099	0.76 (0.70 to 0.82)	0.64 (0.45 to 0.83)
SCORE	368	17 136	446	17 136	0.82 (0.71 to 0.95)	0.50 (0.15 to 0.85)
Pooled analysis						
All	2361	137 493	2985	137 459	0.79 (0.75 to 0.83)	0.51 (0.40 to 0.63)
Location						
Distal	1249	137 493	1838	137 459	0.68 (0.63 to 0.73)	0.48 (0.39 to 0.57)
Women	477	69 726	656	69 773	0.72 (0.64 to 0.81)	0.29 (0.18 to 0.39)
Men	772	67 767	1182	67 686	0.65 (0.60 to 0.72)	0.69 (0.54 to 0.84)
Proximal	1066	137 493	1123	137 459	0.94 (0.87 to 1.03)	0.05 (−0.02 to 0.13)
Women	529	69 726	544	69 773	0.97 (0.86 to 1.09)	0.03 (−0.07 to 0.13)
Men	537	67 767	579	67 686	0.92 (0.81 to 1.03)	0.08 (−0.03 to 0.19)
CRC mortality						
Trial						
NORCCAP	92	13 638	115	13 637	0.79 (0.60 to 1.05)	0.19 (−0.04 to 0.42)
PLCO	171	49 621	182	49 587	0.94 (0.75 to 1.16)	0.03 (−0.05 to 0.11)
UKFSST	291	57 098	399	57 099	0.72 (0.62 to 0.84)	0.21 (0.11 to 0.31)
SCORE	107	17 136	131	17 136	0.81 (0.62 to 1.06)	0.15 (−0.03 to 0.33)
Pooled analysis						
All	661	137 493	827	137 459	0.80 (0.72 to 0.88)	0.13 (0.07 to 0.19)
Location§						
Distal	174	80 395	234	80 360	0.74 (0.61 to 0.90)	0.08 (0.03 to 0.14)
Proximal	169	80 395	177	80 360	0.95 (0.77 to 1.17)	0.01 (−0.04 to 0.06)

CRC = colorectal cancer; NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening; SCORE = Screening for Colon Rectum; UKFSST = UK Flexible Sigmoidoscopy Screening Trial.
* Age at enrollment was 55 to 64 y. Results of χ^2 test on trial (subgroup) rate ratio difference: $P_{incidence} = 0.64$; $P_{mortality} = 0.30$.
† Invited to screening vs. usual care group.
‡ Per 100 persons.
§ Without data from the UKFSST trial.

incidence and mortality remained largely unchanged when each of the 4 trials was removed from analyses. An exception was the removal of the PLCO trial, which led to a greater reduction in CRC incidence in women aged 60 to 64 years (IRR without PLCO, 0.84 [CI, 0.74 to 0.97]) than found in the main analysis (IRR, 0.91 [CI, 0.81 to 1.01]). When we included the age groups 50 to 54 years (from NORCCAP) and 65 to 74 years (from PLCO), the results did not differ substantially from the main results (**Supplement Table 2**, available at Annals.org). Incidence of CRC in the NORCCAP trial was the only statistically significant difference in screening effect on CRC incidence or mortality for women and men between the individual trials (**Supplement Table 3**, available at Annals.org).

DISCUSSION

Our pooled analysis of all 4 randomized trials to assess the long-term benefits of sigmoidoscopy screening for CRC shows that a single screening examination with sigmoidoscopy is effective in reducing CRC incidence in women and men, although the screening benefits seem to be less in women than men. We also found a reduction in all-cause mortality overall and in men.

The best age for endoscopic CRC screening is uncertain, as well as how often screening should be repeated. Current guidelines recommend starting screening at age 45, 50, or 55 years and repeating sigmoidoscopy every 5 years and colonoscopy every 10 years, based on expert opinion and modeling (2). Our study indicates that there is a long-term reduction in CRC incidence and mortality after 1 sigmoidoscopy (participants in the PLCO trial received 2 sigmoidoscopy examinations, but results did not change when PLCO was excluded), which may prompt guideline makers to reconsider endoscopic screening intervals.

Our results are based on intention-to-treat analyses of randomized trials, which means that selection bias was minimized. However, the real benefits of sigmoidoscopy screening may be larger than reported here because of nonadherence in the screening group and contamination in the usual care group (6, 8). Because it is difficult to disentangle real screening benefits from biases in per protocol analyses, even with up-to-date causal inference methodology (9), we believe that the presented intention-to-treat analyses provide the most valid results currently achievable.

Our results show that sigmoidoscopy screening benefits are smaller for women than men. Possible explanations for this difference include differences in the quality of bowel preparation, more technically challenging procedures in women, and a higher incidence and larger proportion of proximal colon cancer in women (10–14). Adherence to sigmoidoscopy screening was also slightly

lower in women than men in all trials except NORCCAP. Colonoscopy contamination of the usual care groups may also differ if thresholds for symptoms triggering a colonoscopy vary between women and men. The idea of sigmoidoscopy with subsequent colonoscopy for patients with findings in the distal colon is to reserve the most invasive and resource-demanding procedure (colonoscopy) for patients with the assumed highest risk. The concept of sigmoidoscopy is thus similar to that of screening using fecal testing, although sigmoidoscopy is also a preventive screening tool itself, through which polyps can be detected and removed, thereby reducing CRC incidence.

In a Polish colonoscopy screening study, the number needed to screen to detect 1 case of advanced neoplasia was similar between each female age group and men 10 years younger (15). A large study involving 12 countries showed the same trend: CRC incidence rates were similar in women and men when women were 4 to 8 years older (16). Colonoscopy screening, instead of sigmoidoscopy as done in the trials in our analysis, might have a more similar effect in women and men. Ongoing colonoscopy screening trials will hopefully answer this question, but results are not expected for another 5 to 10 years (17).

Mathematical models suggest an increased prevalence of proximal adenomas (12, 13, 18) and an increased proportion of proximal CRC cases (4) with increasing age. The effect of sigmoidoscopy screening at 15-year follow-up was mainly confined to the distal colon. The lack of effect in the proximal colon differs from findings of our previous meta-analysis of 3 sigmoidoscopy trials (4), where we also documented a small incidence reduction in the proximal colon. However, the current pooled analysis includes all 4 sigmoidoscopy trials and has a longer follow-up, which means that results may not be directly comparable.

Methodology differs among the 4 trials. While the Norwegian trial randomly assigned participants directly from the population registry, the other 3 trials randomly assigned only persons who had expressed interest in participating. Further, because of more stringent positivity thresholds, fewer participants in the U.K. and Italian trials were referred to colonoscopy. Finally, the U.S. trial offered 2 sigmoidoscopy screening examinations, but benefits were similar to those seen in the other 3 trials, which used once-only screening. Despite these differences, the reductions in CRC incidence and mortality were similar among the trials. Of note, these differences do not seem to influence effectiveness, because CRC incidence and mortality reductions were similar in all trials (5–8).

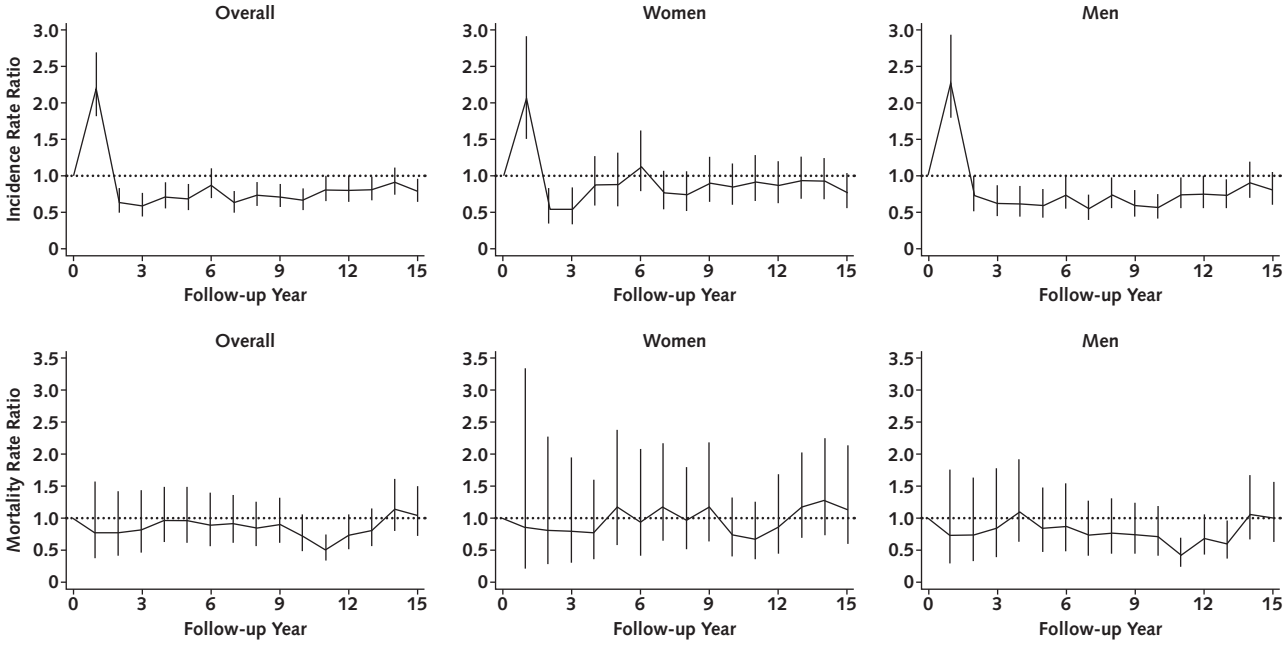
The main strengths of our study are the large number of persons included, the long follow-up, the access to detailed data that have not previously been published, and the expertise from all study groups. Limitations include less granular data from the U.K. trial due to privacy regulations, differences in end point acquisition procedures among the 4 trials, and lack of analysis on confounding variables for adjusted per protocol analyses.

Table 3. Pooled Analysis of CRC Incidence and Mortality in Randomized Sigmoidoscopy Screening Trials for Women and Men and by Age Group at Enrollment

Variable	Screening, *n*		Usual Care, *n*		Intention-to-Screen Analysis (95% CI)*		
	Cases	Participants	Cases	Participants	Rate Ratio	Rate Difference†	*P* Value‡
CRC incidence							
Sex							0.032
Women	1020	69 726	1205	69 773	0.84 (0.77 to 0.91)	0.29 (0.15 to 0.44)	
Men	1341	67 767	1780	67 686	0.75 (0.70 to 0.81)	0.75 (0.56 to 0.93)	
Age group							0.169
55–59 y	1012	71 339	1344	71 681	0.75 (0.69 to 0.82)	0.50 (0.36 to 0.65)	
60–64 y	1349	66 154	1641	65 778	0.81 (0.76 to 0.87)	0.53 (0.34 to 0.71)	
Women, by age group							0.040
55–59 y	423	36 408	557	36 671	0.76 (0.67 to 0.87)	0.39 (0.20 to 0.57)	
60–64 y	597	33 318	648	33 102	0.91 (0.81 to 1.01)	0.20 (−0.03 to 0.43)	
Men, by age group							0.93
55–59 y	589	34 931	787	35 010	0.75 (0.67 to 0.83)	0.63 (0.40 to 0.86)	
60–64 y	752	32 836	993	32 676	0.75 (0.68 to 0.83)	0.88 (0.59 to 1.17)	
CRC mortality							
Sex							0.025
Women	281	69 726	305	69 773	0.91 (0.77 to 1.17)	0.04 (−0.03 to 0.11)	
Men	380	67 766	522	67 686	0.73 (0.64 to 0.83)	0.24 (0.14 to 0.34)	
Age group							0.60
55–59 y	280	71 338	364	71 681	0.77 (0.65 to 0.90)	0.13 (0.05 to 0.20)	
60–64 y	381	66 154	463	65 778	0.81 (0.71 to 0.93)	0.14 (0.05 to 0.24)	
Women, by age group							0.26
55–59 y	114	36 408	139	36 671	0.82 (0.64 to 1.07)	0.07 (−0.02 to 0.16)	
60–64 y	167	33 318	166	33 102	0.99 (0.79 to 1.23)	0.01 (−0.11 to 0.12)	
Men, by age group							0.83
55–59 y	166	34 930	225	35 010	0.72 (0.59 to 0.89)	0.19 (0.07 to 0.31)	
60–64 y	214	32 836	297	32 676	0.72 (0.60 to 0.86)	0.29 (0.14 to 0.45)	

CRC = colorectal cancer.
* Invited to screening vs. usual care group.
† Per 100 persons.
‡ χ^2 test on homogeneity in subgroup rate ratios.

Figure 3. Yearly rate ratios in incidence (*top*) and mortality (*bottom*) for CRC, by year since sigmoidoscopy screening, for all participants and for women and men separately.



Age at enrollment was 55 to 64 y. Dotted horizontal lines indicate no difference between participants in screening and usual care groups. Gray vertical lines represent 95% CIs of yearly estimated incidence and mortality rate ratios. CRC = colorectal cancer.

In conclusion, our pooled analysis of all 4 large randomized trials of sigmoidoscopy screening demonstrates a significant and sustained effect of sigmoidoscopy on CRC incidence and mortality for 15 years.

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