ORIGINAL ARTICLE

Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

M. Bretthauer, M. Løberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminski, for the NordICC Study Group*

ABSTRACT

BACKGROUND

Although colonoscopy is widely used as a screening test to detect colorectal cancer, its effect on the risks of colorectal cancer and related death is unclear.

METHODS

We performed a pragmatic, randomized trial involving presumptively healthy men and women 55 to 64 years of age drawn from population registries in Poland, Norway, Sweden, and the Netherlands between 2009 and 2014. The participants were randomly assigned in a 1:2 ratio to either receive an invitation to undergo a single screening colonoscopy (the invited group) or to receive no invitation or screening (the usual-care group). The primary end points were the risks of colorectal cancer and related death, and the secondary end point was death from any cause.

RESULTS

Follow-up data were available for 84,585 participants in Poland, Norway, and Sweden — 28,220 in the invited group, 11,843 of whom (42.0%) underwent screening, and 56,365 in the usual-care group. A total of 15 participants had major bleeding after polyp removal. No perforations or screening-related deaths occurred within 30 days after colonoscopy. During a median follow-up of 10 years, 259 cases of colorectal cancer were diagnosed in the invited group as compared with 622 cases in the usual-care group. In intention-to-screen analyses, the risk of colorectal cancer at 10 years was 0.98% in the invited group and 1.20% in the usual-care group, a risk reduction of 18% (risk ratio, 0.82; 95% confidence interval [CI], 0.70 to 0.93). The risk of death from colorectal cancer was 0.28% in the invited group and 0.31% in the usual-care group (risk ratio, 0.90; 95% CI, 0.64 to 1.16). The number needed to invite to undergo screening to prevent one case of colorectal cancer was 455 (95% CI, 270 to 1429). The risk of death from any cause was 11.03% in the invited group and 11.04% in the usual-care group (risk ratio, 0.99; 95% CI, 0.96 to 1.04).

CONCLUSIONS

In this randomized trial, the risk of colorectal cancer at 10 years was lower among participants who were invited to undergo screening colonoscopy than among those who were assigned to no screening. (Funded by the Research Council of Norway and others; NordICC ClinicalTrials.gov number, NCT00883792.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Bretthauer can be contacted at michael.bretthauer@medisin.uio.no or at the Clinical Effectiveness Research Group, University of Oslo, Postbox 1089, Blindern, N-0318 Oslo, Norway.

*The members of the NordICC Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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As the third most common type of cancer and the second leading cause of death from cancer worldwide, colorectal cancer is an attractive target for population screening.[1] Multiple screening options are available, but high-quality evidence to indicate the best strategies is limited.[2] The most commonly used screening tests are fecal testing for occult blood and endoscopic screening with sigmoidoscopy or colonoscopy.[3]

In randomized trials, the relative risk of death from colorectal cancer was approximately 15% lower among persons who were assigned to undergo screening with guaiac fecal testing than among those who were assigned to no screening; however, screening with this test had little or no effect on the risk of colorectal cancer.[3] Because most colorectal cancers develop from benign polyps that can be detected and removed during endoscopy, endoscopic screening may prevent colorectal cancer. In a pooled analysis of three randomized trials, the incidence of colorectal cancer was up to 25% lower after 10 to 12 years of follow-up among persons who had been invited to undergo sigmoidoscopy screening than among those who had not been invited.[4]

Colonoscopy is considered to be more effective than sigmoidoscopy because it can be used to examine the entire large bowel.[3,5] Thus, sigmoidoscopy has largely been replaced by colonoscopy, which is the predominant screening test for colorectal cancer in the United States and is recommended to be performed every 10 years.[5] In contrast, colonoscopy has not been adopted in many other parts of the world, partly because evidence from randomized trials regarding the benefits of this test is lacking.[6]

A balance among benefits, harms, and cost-effectiveness of various colorectal cancer screening tests is important because colonoscopy is more invasive and burdensome for patients than fecal testing and sigmoidoscopy, and it requires more clinical resources. Here, we report the results of the Nordic-European Initiative on Colorectal Cancer (NordICC), a large, multicenter, randomized trial that investigated the effects of population-based colonoscopy screening on the risks of colorectal cancer and related death at 10 years.

METHODS

TRIAL DESIGN

The pragmatic NordICC trial was conducted in Poland, Norway, Sweden, and the Netherlands. The trial design and rationale have been described in detail previously.[7,8] Eligible participants were men and women 55 to 64 years of age who had not previously undergone screening and who lived in one of the four countries where the trial was conducted. Exclusion criteria were death or the diagnosis of colorectal cancer before trial entry, as assessed in national registries before randomization.[7,8] Participants were identified directly from the population registries in the four countries and were randomly assigned in a 1:2 ratio to either invitation to undergo colonoscopy screening (the invited group) or to no invitation and no screening (the usual-care group). Independent organizations in each participating country randomly assigned participants with the use of a computer-generated allocation algorithm, stratified according to age, sex, and municipality.[8] Screening was performed between June 8, 2009, and June 23, 2014, as reported previously.[8]

At the beginning of the trial, Poland had an opportunistic screening program for colorectal cancer in some geographic areas but not in the area where the trial was conducted. In the other countries, no organized colorectal cancer screening of any kind was available at the beginning of the trial. During the last 4 years of trial follow-up, colorectal cancer screening was gradually introduced according to region and age group in the participating countries.

The integrity of the trial was preserved through collaboration with the screening programs in two ways. First, screening programs were introduced earlier in geographic areas where the trial was not enrolling participants, and second, the trial participants were too old to be eligible for the new screening programs by the time the programs were introduced in the areas where our trial was being conducted. Thus, none of the participants who were enrolled in the trial were eligible for any colorectal cancer screening programs outside the trial during screening or follow-up.[8] Throughout the trial, we monitored opportunistic colonoscopy screening activity in the trial areas and did not

identify additional colonoscopy procedures beyond what would have been expected for clinical indications.[9]

This report is based on follow-up data from all 84,585 participants in Poland, Norway, and Sweden (89.1% of all 94,959 participants, including those from the Netherlands, who were originally included in the trial)[8] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Of the remaining 10,374 participants, 594 had been excluded, and data from the remaining 9780 participants, all from the Netherlands, could not be included because Statistics Netherlands could not provide follow-up data from the usual-care group owing to a new Dutch law based on the recently introduced European Union General Data Protection Regulation. To ensure timely reporting of prespecified end-point analyses, we decided to submit this report for publication without data from the Netherlands.

The trial was funded by research grants in the participating countries. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the statistical analysis plan at NEJM.org.

INTERVENTIONS

Participants were randomly assigned to either invitation to one-time screening colonoscopy or to no invitation to screening, as previously described.[7] All screening colonoscopies were performed at dedicated centers.[7,8] A quality-assurance and training program was implemented for the trial.[7] All lesions detected during colonoscopy were removed if feasible, and all tumors were biopsied. Participants in whom cancer was detected on screening were referred from the trial centers to the public health service and treated in accordance with national policies. Dedicated histopathologists assessed all polyps and cancers according to the classification of the World Health Organization.[10] Data from all screening examinations were registered in an online electronic case-report form and stored at a central database. Patients were referred for surveillance of polyps after screening in accordance with national guidelines (see the Supplementary Appendix).[7]

TRIAL END POINTS

The primary end points were the risks of colorectal cancer and death from colorectal cancer after a median follow-up of 10 to 15 years (with the first analysis planned after 10 years).[7] The secondary end point was death from any cause. A diagnosis of colorectal cancer was defined, according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, as cancer in the colon or rectum (topography codes C18 to C20, combined with International Classification of Diseases for Oncology morphology codes for adenocarcinoma) (see the Supplementary Appendix). The stage of colorectal cancer was classified as early-stage (Dukes' stage A or B), late-stage (Dukes' stage C or D), or unknown. Tumors with a histopathological diagnosis other than adenocarcinoma were not counted as events. Colorectal cancer–related deaths were defined as those that were listed as such in the cause-of-death registries in the participating countries.

FOLLOW-UP

Almost complete long-term follow-up of all participants who underwent randomization was made possible through the use of unique personal identification numbers, which were linked to cancer registries and cause-of-death registries, for all trial participants in each country.[7] All participants who underwent randomization were followed for all end-point events through these registries, regardless of whether they underwent screening.

ETHICS AND CONSENT

This randomized trial followed a pragmatic design; the participants underwent randomization before they were asked whether they wanted to participate in the trial (in the invited group) or not asked to participate (the usual-care group).[7,11] All the participants who underwent colonoscopy screening provided written informed consent. With the exception of a subsample of 6900 participants in Norway, the participants in the usual-care group were not informed about their enrollment in the trial at inclusion or during follow-up. During follow-up, the subsample of participants in Norway received a questionnaire related to lifestyle and general health.[12] The trial was approved by the ethics committees at all

participating centers, the Swedish National Council on Medical Ethics, and the Health Council of the Netherlands.[7]

STATISTICAL ANALYSIS

The sample-size calculation was based on intention-to-screen analyses and has been described in detail previously.[7] We estimated that event rates based on colorectal cancer–related mortality after 15 years would provide enough power to also assess the risk of colorectal cancer.[7] We assumed a 25% difference in colorectal cancer–related mortality between the invited group and the usual-care group, a 50% participation rate, and 50% screening efficacy.[7] With 80% power at a two-sided significance level of 5%, we calculated that at least 22,800 participants in the invited group and 45,600 participants in the usual-care group would be needed. In Poland, because of the availability of resources and lower-than-anticipated participation in screening, we enrolled a higher number of participants than the number we had planned in order to maintain statistical power.

The primary analysis was conducted in accordance with the intention-to-screen principle. Follow-up time was measured from the date of randomization to the date of emigration, the diagnosis of colorectal cancer (for analyses of the risk of colorectal cancer), death from colorectal cancer (for analyses of death from colorectal cancer), or death from causes other than colorectal cancer or to the end of follow-up after 10 years, whichever came first. We did not use Cox proportional-hazards models for analyses, as originally planned, because of the nonproportional hazards of the risk of colorectal cancer during follow-up.[13,14] We used the Kaplan–Meier estimator to calculate the cumulative 10-year risks of colorectal cancer and colorectal cancer–related death in the invited group and the usual-care group, and we compared risks using risk ratios, risk differences, and annual incidence rate ratios. We performed analyses in which competing events (i.e., death from causes other than colorectal cancer) were considered to be censoring events, and we performed additional analyses in which competing events were not treated as censoring events.[15] The competing events were unlikely to affect the results, and the current report focuses on analyses in which deaths from causes other than colorectal cancer were treated as censoring events. Bootstrapping was used to calculate 95% confidence intervals. The number needed to invite to undergo screening to prevent one case of colorectal cancer was calculated as the reciprocal of the between-group difference in risk with respect to the risk of colorectal cancer at 10 years.

We estimated the per-protocol effect of screening, which was defined as the effect of screening if all the participants who were randomly assigned to the invited group had undergone screening.[14] The risk of colorectal cancer may have differed between the participants who underwent screening and those who were invited to undergo screening but declined to do so; therefore, our analyses adjusted for the baseline covariates of the participants (Table S2). We estimated standardized risks with the use of a pooled logistic model with the following covariates: age at randomization (with the use of restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles), sex (male or female), country (Poland, Norway, or Sweden), group assignment (invited or usual care), duration of follow-up (with the use of restricted cubic splines with knots at 3-month periods at 2, 4, 6, and 8 years), and product terms representing interactions between group assignment and duration of follow-up.[14] We did not observe opportunistic screening of any meaningful extent in the usual-care group and thus did not adjust for it in the per-protocol analyses. In a sensitivity analysis, we used the approach that was proposed by Cuzick et al.[16] and previously used in other trials of colorectal cancer screening (see Table S6).[17,18]

RESULTS

PARTICIPANTS

The trial included 54,927 eligible participants from Poland, 26,588 from Norway, and 3664 from Sweden. After randomization and before the beginning of the intervention, 175 participants who were assigned to the invited group and 419 of those who were assigned to the usual-care group were excluded because they had died or had received a diagnosis of colorectal cancer at randomization but had not yet been identified as such in the registries at the time. Thus, the current analyses involved 84,585 participants (28,220 in the invited group and 56,365

Table 1. Characteristics of the Trial Participants.

Characteristic	All Participants (N = 84,585)	Participants in Norway (N = 26,411)	Participants in Poland (N = 54,258)	Participants in Sweden (N = 3646)
Group — no.				
Invited	28,220	8,815	18,184	1221
Usual care	56,365	17,596	36,344	2425
Sex — no.				
Female	42,186	13,194	27,330	1662
Male	42,399	13,217	27,198	1984
Age at randomization — no.				
55–59 yr	43,100	12,524	28,792	1784
60–64 yr	41,485	13,887	25,736	1862
Screening participation — no./total no. (%)				
Women and men	11,843/28,220 (42.0)	5354/8815 (60.7)	6003/18,184 (33.0)	486/1221 (39.8)
Women	5,724/14,066 (40.7)	2580/4390 (58.8)	2918/9117 (32.0)	226/559 (40.4)
Men	6,119/14,154 (43.2)	2774/4425 (62.7)	3085/9067 (34.0)	260/662 (39.3)
55–59 yr	5,877/14,369 (40.9)	2497/4174 (59.8)	3173/9599 (33.1)	207/596 (34.7)
60–64 yr	5,966/13,851 (43.1)	2857/4641 (61.6)	2830/8585 (33.0)	279/625 (44.6)
Screening performance — no./total no. (%)				
Good or very good bowel preparation*	110,610/11,635 (91.2)	4739/5174 (91.6)	5445/5999 (90.8)	426/462 (92.2)
Cecum intubation	11,470/11,843 (96.8)	5130/5354 (95.8)	5868/6003 (97.8)	472/486 (97.1)
Adenoma detection	3,634/11,843 (30.7)	1453/5354 (27.1)	2111/6003 (35.2)	70/486 (14.4)
Screening-related adverse events — no./total no. (%)				
Perforation†	0	0	0	0
Major bleeding‡	15/11,843 (0.13)	8/5354 (0.15)	7/6003 (0.12)	0

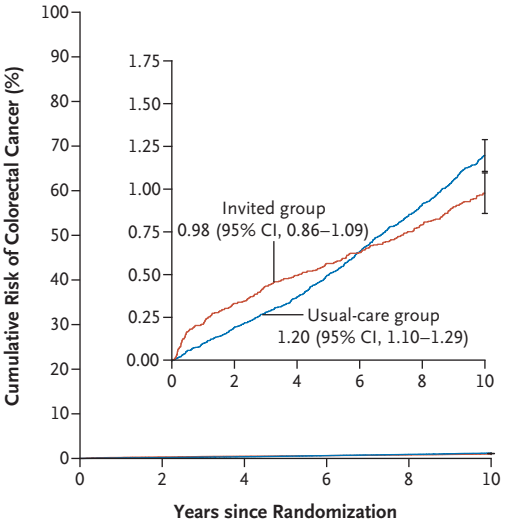
* Data in this category were missing for 208 participants, including some for whom data on the bowel preparation regimen were missing and others for whom data on the quality of bowel preparation were missing.
† One perforation that occurred in a participant in the Netherlands was not included in these analyses.[8]
‡ Major bleeding was defined as bleeding that warranted treatment. All cases of major bleeding were treated endoscopically, and further therapy was not warranted.

in the usual-care group); 42,399 (50.1%) were men and 42,186 (49.9%) were women (Table 1). The median age at randomization was 59 years (Table S3). The median follow-up for the current analysis was 10.0 years in both groups (interquartile range, 9.9 to 10.0; maximum follow-up, 10.0 years).

COLONOSCOPY SCREENING

The percentage of participants who underwent screening varied among the countries (from 33.0% in Poland to 60.7% in Norway) and was higher overall among men than among women and among older participants than among younger participants (Table 1). The cecum was intubated in 96.8% of the colonoscopies performed, and the quality of bowel preparation was adequate in more than 90% of the colonoscopies.[8]

Colorectal cancer was diagnosed at screening in 62 participants (0.5% of those who underwent screening). These 62 cases included 2 cases in Poland that had been classified as adenomas in our previous analysis (see the Supplementary Appendix).[8] Adenomas were detected and removed at screening in 3634 participants (30.7% of those who underwent screening). A total of 15 participants (0.13%) had polypectomy-related



No. at Risk						
Invited group	28,220	27,684	27,111	26,461	24,000	18,748
Usual-care group	56,365	55,375	54,192	52,819	47,769	37,313

Figure 1. Cumulative Risk of Colorectal Cancer at 10 Years in Intention-to-Screen Analyses.

The inset shows the same data on an enlarged y axis. I bars indicate 95% confidence intervals.

major bleeding; all cases of bleeding were treated endoscopically and did not warrant further interventions (Table 1). No perforations or screening-related deaths occurred within 30 days after screening.

INCIDENCE OF COLORECTAL CANCER

The risk of colorectal cancer at 10 years was 0.98% (259 cases) in the invited group and 1.20% (622 cases) in the usual-care group, for a risk ratio of 0.82 (95% confidence interval [CI], 0.70 to 0.93) (Fig. 1 and Table 2). Table S5 shows the risks and risk ratios of colorectal cancer in Norway (risk ratio, 0.76) and Poland (risk ratio, 0.84). Figure 2 shows the yearly incidence rate ratios in the invited group as compared with the usual-care group. The number needed to invite to undergo screening to prevent one case of colorectal cancer within 10 years was 455 (95% CI, 270 to 1429). Among the participants with cases of colorectal cancer for which staging information was available, 0.38% in the invited group and 0.44% in the usual-care group received a diagnosis of early-stage (stage A or B) colorectal cancer, whereas 0.40% in the invited group and 0.50% in the usual-care group received a diagnosis of late-stage (stage C or D) colorectal cancer (Table S7). Analyses in which competing events were not treated as censoring events showed results that were similar to those in the main analysis (Table S1).

COLORECTAL CANCER–RELATED DEATH AND DEATH FROM ANY CAUSE

The risk of colorectal cancer–related death at 10 years was 0.28% (72 deaths) among participants in the invited group and 0.31% (157 deaths) among those in the usual-care group (risk ratio, 0.90; 95% CI, 0.64 to 1.16) (Table 2 and Fig. 3). During the 10-year follow-up period, 3036 participants in the invited group (11.03%) died from any cause, as compared with 6079 (11.04%) in the usual-care group (risk ratio, 0.99; 95% CI, 0.96 to 1.04) (Table 2).

ADJUSTED PER-PROTOCOL ANALYSES

In adjusted analyses to estimate the effect of screening if all the participants who were randomly assigned to screening had actually undergone screening, the risk of colorectal cancer at 10 years was decreased from 1.22% to 0.84%, corresponding to an estimated risk ratio of 0.69 (95% CI, 0.55 to 0.83) (Table S4 and Fig. S3). The results were similar in the sensitivity analysis (Table S6). The corresponding risk ratio was 0.55 (95% CI, 0.38 to 0.74) in Norway and 0.85 (95% CI, 0.63 to 1.12) in Poland (Table S5).

The risk of death from colorectal cancer was 0.15% in the invited group and 0.30% in the usual-care group. The estimated risk ratio was 0.50 (95% CI, 0.27 to 0.77) (Fig. S4). In the sensitivity analysis, the risk ratio was 0.72, but the estimate was imprecise (95% CI, 0 to 3.70).

DISCUSSION

In our large, population-based, randomized trial, the risk of colorectal cancer at 10 years was 0.98% among participants who were invited to undergo colonoscopy screening, as compared with 1.20% among those who were assigned to receive usual care. Colonoscopy screening was performed in only 42% of the participants who were invited to undergo screening. In adjusted analyses to estimate the effect of screening if all the participants who were randomly assigned to screening had actually undergone screening, the

Table 2. Primary and Secondary End Points.

End Point	Invited Group		Usual-Care Group		Risk Difference (95% CI)	Risk Ratio (95% CI)
	Participants	10-Yr Risk (95% CI)	Participants	10-Yr Risk (95% CI)		
	number	*percent*	*number*	*percent*	*percentage points*	
Colorectal cancer	259	0.98 (0.86 to 1.09)	622	1.20 (1.10 to 1.29)	−0.22 (−0.37 to −0.07)	0.82 (0.70 to 0.93)
Death						
From colorectal cancer	72	0.28 (0.21 to 0.34)	157	0.31 (0.26 to 0.35)	−0.03 (−0.11 to 0.05)	0.90 (0.64 to 1.16)
From any cause	3036	11.03 (10.66 to 11.40)	6079	11.04 (10.78 to 11.30)	−0.01 (−0.47 to 0.44)	0.99 (0.96 to 1.04)

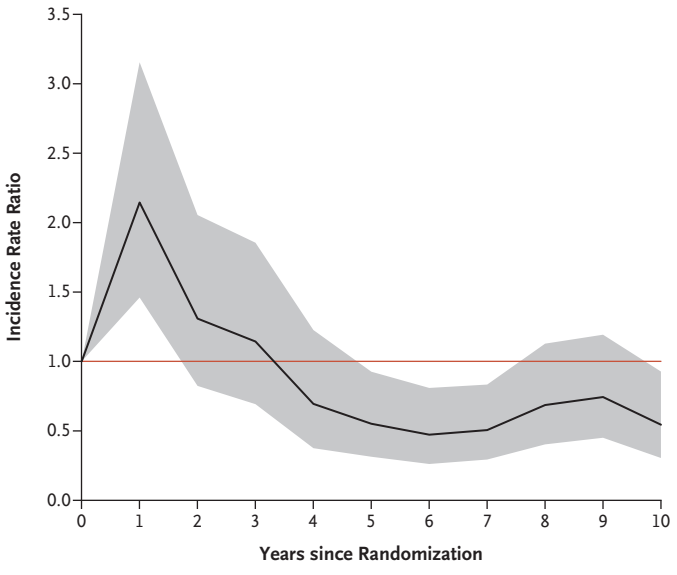


Figure 2. Incidence Rate Ratios for Colorectal Cancer in the Invited Group as Compared with the Usual-Care Group in Intention-to-Screen Analyses.
The shaded area indicates 95% confidence intervals. The usual-care group served as the reference group (red horizontal line).

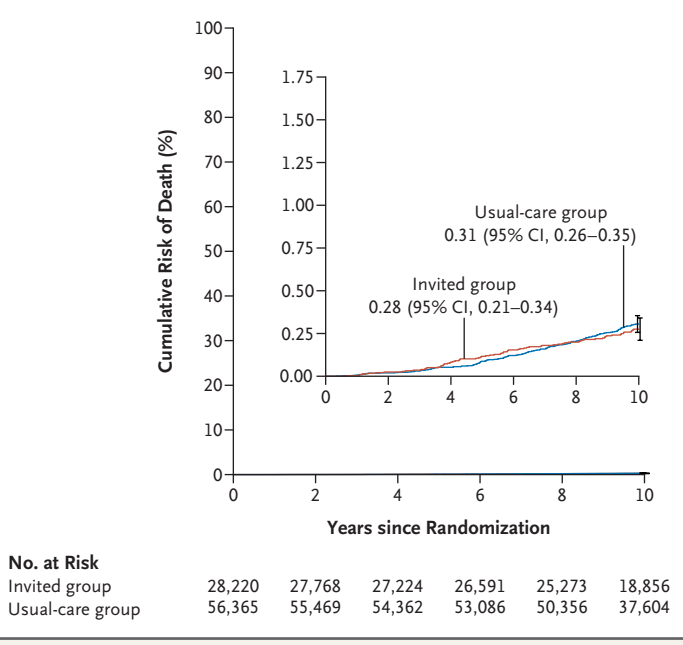


Figure 3. Cumulative Risk of Death from Colorectal Cancer at 10 Years in Intention-to-Screen Analyses.
The inset shows the same data on an enlarged y axis. I bars indicate 95% confidence intervals.

risk of colorectal cancer was decreased from 1.22% to 0.84%, and the risk of colorectal cancer–related death was decreased from 0.30% to 0.15%. Our results may serve to quantify the effectiveness of screening colonoscopy for the prevention of colorectal cancer and thus enable decision makers to properly prioritize resources for cancer screening and health care services.

The overall aim of our trial was to quantify the benefits of colonoscopy in population screening. Therefore, we chose a pragmatic trial design with consent after randomization; this design best mimics a population screening program. A downside of this approach is that participation in screening cannot be artificially enriched as in some sigmoidoscopy trials,[4] and thus the benefits of screening may be underestimated.[7] To address this issue, we performed per-protocol analyses with adjustments for potential confounders.[14] Our estimates of a 31% decrease in the risk of colorectal cancer and a 50% decrease in colorectal cancer–related death (if all the participants who were eligible for colonoscopy screening had undergone screening) probably underestimated the benefit because, as in most other large-scale trials of colorectal cancer screening, we could not adjust for all important confounders in all countries.[17,18] In fact, even though a 31% decrease in the risk of colorectal cancer is a clinically relevant benefit, it is lower than that anticipated in clinical guidelines based on observational and modeling studies[5,19,20] and similar to the estimates in trials of sigmoidoscopy screening, which have shown a decrease in the risk of colorectal cancer of 23 to 24% in intention-to-treat analyses and 33 to 40% in adjusted per-protocol analyses after a similar follow-up time.[21-24] Thus, these results suggest that colonoscopy screening might not be substantially better in reducing the risk of colorectal cancer than sigmoidoscopy. Future analyses of our trial results may provide more precise estimates of the per-protocol effects of colonoscopy screening for comparison purposes with other screening tests.

Owing to the nature of colonoscopy as a preventive screening test and the nature of colorectal cancer, the benefits of endoscopic screening with respect to the risk of colorectal cancer are expected to be apparent earlier than those with respect to death related to this disease. Also, the number of cases of colorectal cancer is expected to be higher than the number of colorectal cancer–related deaths during the early part of the follow-up period.[17,18,21] The lack of a significant screening benefit with respect to colorectal cancer–related death in intention-to-treat analyses should therefore be interpreted in this context. Optimism related to the effects of screening on colorectal cancer–related death may be warranted in light of the 50% decrease observed in adjusted per-protocol analyses.

Although we observed appreciable reductions in relative risks, the absolute risks of the risk of colorectal cancer and even more so of colorectal cancer–related death were lower than those in previous screening trials and lower than what we anticipated when the trial was planned.[7,21] This finding may reflect both a declining risk of colorectal cancer observed in many countries in recent years and an appreciable improvement in the prognosis of colorectal cancer owing to better treatment options. Thus, our estimation of the number needed to invite to screening to prevent one case of colorectal cancer was higher than that in the older sigmoidoscopy trials, although the relative effects were similar.[21-24] These findings underscore the importance of absolute risks and effects when planning cancer screening programs. Comparative absolute benefits as well as harms and the burden of colonoscopy, sigmoidoscopy, and other screening tests should be discussed with patients with the use of shared decision making to find the best test on the basis of personal values and preferences.[20]

Owing to the small number of events at the 10-year follow-up, we did not include analyses of distal as compared with proximal cancer, sex, or age at screening. Continued follow-up in our trial and analyses of other ongoing trials may provide clarity regarding differences with respect to distal as compared with proximal cancers, as well as benefits of screening colonoscopy after 10 years in women and men.[25-27]

In the countries with the most participants in the trial, the percentage of participants in the invited group who underwent screening was higher in Norway (61%) than in Poland (33%). In intention-to-screen analyses, the screening benefit was similar in the two countries (risk ratios, 0.76 and 0.84, respectively), but in adjusted per-protocol analyses, this benefit was estimated to be greater in Norway than in Poland (risk ratios, 0.55 and 0.85, respectively). Confidence intervals

were overlapping, and event rates were small; thus, no firm conclusions can be drawn. However, two differences between Norway and Poland warrant attention in interpreting our results. First, the absolute risk of colorectal cancer in the usual-care group was higher in Norway than in Poland. The results of trials of sigmoidoscopy screening suggest that relative screening benefits may be smaller with a smaller risk of colorectal cancer.[4] Second, although the risk of colorectal cancer in the usual-care group was lower in Poland than in Norway in our trial, we observed a high rate of detection of colorectal cancer at screening in Poland (Fig. S2C), findings that indicate a strong tendency of participants with a high risk of colorectal cancer in the invited group to undergo screening. In Norway, such a tendency was not observed, which explains the larger effect of adjustment with respect to adherence in Norway than in Poland.

The strengths of our trial are its originality, its randomized design and considerable size, the fact that participants had not previously undergone screening, and the minimal-to-nil screening contamination of the control group. Training programs for endoscopists were implemented, and quality indicators were monitored throughout the trial, as previously reported.[8] Finally, follow-up was virtually complete and the accuracy of classification of causes of death was considered to be high in all the participating countries.[8]

The limitations of our trial include lower-than-expected participation in some countries and a lack of information about adherence to recommendations regarding surveillance for polyps. The previously reported variation in quality indicators among endoscopists may have resulted in differences in the detection of cancer after screening, but event rates were too small to investigate further.[8] Admittedly, enrollment of a population-based sample probably entails lower participation than a trial with randomization preceded by informed consent. However, our design should produce a more realistic estimate of benefits and harms in real-life screening programs. Although we adhered to the protocol by reporting the first results at this time, longer follow-up may be needed to capture the full effect of colonoscopy screening.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Michael Bretthauer, M.D., Ph.D., Magnus Løberg, M.D., Ph.D., Paulina Wieszczy, Ph.D., Mette Kalager, M.D., Ph.D., Louise Emilsson, M.D., Ph.D., Kjetil Garborg, M.D., Ph.D., Maciej Rupinski, M.D., Ph.D., Evelien Dekker, M.D., Ph.D., Manon Spaander, M.D., Ph.D., Marek Bugajski, M.D., Ph.D., Øyvind Holme, M.D., Ph.D., Ann G. Zauber, Ph.D., Nastazja D. Pilonis, M.D., Ph.D., Andrzej Mroz, M.D., Ph.D., Ernst J. Kuipers, M.D., Ph.D., Joy Shi, Ph.D., Miguel A. Hernán, M.D., Dr.Ph., Hans-Olov Adami, M.D., Ph.D., Jaroslaw Regula, M.D., Ph.D., Geir Hoff, M.D., Ph.D., and Michal F. Kaminski, M.D., Ph.D.

The authors' affiliations are as follows: the Clinical Effectiveness Research Group (M. Bretthauer, M.L., P.W., M.K., K.G., M. Bugajski, Ø.H., H.-O.A., M.F.K.) and the Department of General Practice, Institute of Health and Society (L.E.), University of Oslo, the Clinical Effectiveness Research Group, Department of Transplantation Medicine, Oslo University Hospital (M. Bretthauer, M.L., M.K., K.G., Ø.H., H.-O.A.), and the Cancer Registry of Norway (G.H.), Oslo, the Institute of Clinical Medicine, University of Tromsø, Tromsø (M. Bretthauer), and the Department of Research and Development, Telemark Hospital, Skien (G.H.) — all in Norway; the Department of Gastroenterological Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (P.W., M.R., M. Bugajski, N.D.P., A.M., J.R., M.F.K.), and the Departments of Pathology (A.M.) and Gastroenterological Oncology (P.W., M.R., M. Bugajski, N.D.P., A.M., J.R., M.F.K.), Medical Center of Postgraduate Education — both in Warsaw, Poland; Vårdcentralen Värmlands Nysäter and the Center for Clinical Research, County Council of Värmland, Karlsdad (L.E.), and the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna (L.E., H.-O.A.) — both in Sweden; the Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, and the University of Amsterdam, Amsterdam (E.D.), and the Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam (M.S., E.J.K.) — all in the Netherlands; the Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York (A.G.Z.); and CAUSALab, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston (J.S., M.A.H.).

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Helsingen LM, Kalager M. Colorectal cancer screening — approach, evidence, and future directions. N Engl J Med Evid 2022. DOI: 10.1056/EVIDra2100035
3. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, et al. The IARC perspective on colorectal cancer screening. N Engl J Med 2018;378:1734-40.
4. Holme Ø, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. BMJ 2017;356:i6673.
5. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325:1965-77.
6. Basu P, Ponti A, Anttila A, et al. Status of implementation and organization of cancer screening in the European Union Member States — summary results from the second European screening report. Int J Cancer 2018;142:44-56.
7. Kaminski MF, Bretthauer M, Zauber AG, et al. The NordICC study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Endoscopy 2012;44:695-702.
8. Bretthauer M, Kaminski MF, Løberg M, et al. Population-based colonoscopy screening for colorectal cancer: a European randomized trial. JAMA Intern Med 2016;176:894.
9. Sykehuset Telemark. Gastronet — colonoscopy center. 2021 (https://www.sthf.no/helsefaglig/gastronet/gastronet-resultater-koloskopi-senter).
10. Hamilton SR, Aaltonen LA, eds. Pathology and genetics of tumors of the digestive tract: World Health Organization classification of tumors, 3rd ed. Lyon, France: IARC Press, 2000;104-19.
11. Løberg M, Kalager M, Bretthauer M. "Randomize, then consent", or "consent, then randomize"? Revitalizing the issue of pre-consent randomization. Epidemiology 2016;27:393-4.
12. Gjøstein DK, Huitfeldt A, Løberg M, et al. Incentives and participation in a medical survey. Tidsskr Nor Laegeforen 2016;136:1082-7.
13. Stensrud MJ, Hernán MA. Why test for proportional hazards? JAMA 2020;323:1401-2.
14. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.
15. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernán MA. A causal framework for classical statistical estimands in failure-time settings with competing events. Stat Med 2020;39:1199-236.
16. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997;16:1017-29.
17. Atkin W, Wooldrage K, Parkin DM, 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;389:1299-311.
18. Senore C, Riggi E, Armaroli P, et al. Long-term follow-up of the Italian flexible sigmoidoscopy screening trial. Ann Intern Med 2022;175:36-45.
19. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.
20. Helsingen LM, Vandvik PO, Jodal HC, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. BMJ 2019;367:l5515.
21. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15.
22. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624-33.
23. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345-57.
24. Segnan N, Armaroli P, Bonelli L, et al. 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.
25. Forsberg A, Westerberg M, Metcalfe C, et al. Once-only colonoscopy or two rounds of faecal immunochemical testing 2 years apart for colorectal cancer screening (SCREESCO): preliminary report of a randomised controlled trial. Lancet Gastroenterol Hepatol 2022;7:513-21.
26. Dominitz JA, Robertson DJ, Ahnen DJ, et al. Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM): rationale for study design. Am J Gastroenterol 2017;112:1736-46.
27. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706.