Long-term effects of colonoscopy screening on colorectal cancer incidence and mortality: a multicountry, population-based randomised controlled trial

*Michal F Kaminski, Mette Kalager, Magnus Løberg, Louise Emilsson, Anna Macios, Faye Samy, Joy Shi, Shona Fielding, Miguel A Hernán, Kjetil Garborg, Maciej Rupinski, Evelien Dekker, Manon Spaander, Øyvind Holme, Ann G Zauber, Nastazja D Pilonis, Joanna Didkowska, Piotr Spychalski, Geir Hoff, Jaroslaw Regula, Hans-Olov Adami, Michael Bretthauer, for the NordICC Study Group**

Summary

Background We previously reported the 10-year effects of colonoscopy screening on colorectal cancer incidence and mortality. Here, we report the effects after 13 years of follow-up.

Methods In this multicountry, population-based randomised controlled trial, 84 583 men and women aged 55–64 years at enrolment from Norway, Poland, and Sweden were randomly allocated (1:2) to colonoscopy screening or no screening and analysed. The primary outcomes were colorectal cancer incidence and mortality after 10–15 years of follow-up in intention-to-screen analyses, with first analysis after 10 years, and repeated every other year or at longer intervals. This trial is registered with ClinicalTrials.gov, NCT00883792, and is ongoing.

Findings At 13 years of follow-up, colorectal cancer incidence was 375 colorectal cancers (1·46%) of 28 217 individuals in the screening group and 912 colorectal cancers (1·80%) of 56 366 individuals in the no-screening group. The risk ratio (RR) was 0·81 (95% CI 0·71–0·90) in intention-to-screen analyses and 0·55 (0·33–0·81) in per-protocol analyses. The risk for proximal colorectal cancer was 129 (0·51%) in the screening group versus 283 (0·56%) in the no-screening group (RR 0·91 [0·71–1·09]), and the risk for distal colorectal cancer was 224 (0·87%) in the screening group versus 563 (1·11%) in the no-screening group (RR 0·79 [0·65–0·89]; interaction p<0·0001). In men, the colorectal cancer risk was 214 (1·69%) of 14 154 in the screening group and 541 (2·19%) of 28 247 in the no-screening group (RR 0·77 [0·64 to –0·88]); in women, the risk was 161 (1·24%) of 14 063 in the screening group versus 371 (1·43%) of 28 119 in the no-screening group (RR 0·87 [0·70 to 1·02]; interaction p<0·0001). Colorectal cancer mortality was 106 (0·41%) of 28 217 in the screening group and 236 (0·47%) of 56 366 in the no-screening group (intention-to-screen RR 0·88 [0·68–1·08], per-protocol RR 0·70 [0·26–1·25]). The observed colorectal cancer mortality in the non-screening group (0·47%) was substantially lower than expected at the time of designing the trial (0·82%).

Interpretation One colonoscopy significantly reduced colorectal cancer incidence but not mortality over 13 years. Colorectal cancer mortality was lower in both study groups than when the trial was designed.

Funding The Norwegian Research Council, the Nordic Cancer Union, the Norwegian Cancer Society, and the Health Fund of South-East Norway.

Introduction

With almost 2 million new cases every year, colorectal cancer is the third most common cancer worldwide.[1] To decrease the burden of colorectal cancer, many countries have introduced screening programmes for the general population.[2] A variety of screening tests for colorectal cancer are available, with colonoscopy being the most frequently used in the USA and in some countries in Europe.[3] Colonoscopy screening was, however, introduced without high-quality evidence from randomised trials, when observational studies and disease modelling indicated that colonoscopy might reduce colorectal cancer incidence and mortality by at least 50% and extend the length of life.[4,5]

In 2022, we reported 10-year results from NordICC, a randomised trial on colonoscopy screening.[6] In intention-to-screen analyses, the risk of colorectal cancer at 10 years was 0·98% in the colonoscopy screening group and 1·20% in the no-screening group, a risk reduction of 18%. Colorectal cancer mortality was, however, not significantly reduced in the colonoscopy screening group. Adjusted per-protocol analyses suggested a reduction in colorectal cancer incidence of 30%, and of up to 50% for colorectal cancer mortality.[6] A 2025 randomised trial in Spain reported that colonoscopy screening yields similar benefits on colorectal cancer incidence and mortality as screening with faecal immunochemical testing, but that trial had no

Lancet 2026; 407: 1787–95

Published Online May 5, 2026 https://doi.org/10.1016/S0140-6736(26)00508-8

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 12, 2026

See Comment page 1758

*Members listed in the appendix (p 3)

Department of Oncological Gastroenterology, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland (Prof M F Kaminski MD PhD, M Rupinski MD, Prof N D Pilonis MD PhD, Prof J Regula MD PhD); **Centre of Postgraduate Medical Education, Warsaw, Poland** (Prof M F Kaminski, M Rupinski, Prof N D Pilonis, Prof J Regula); **Clinical Effectiveness Research Group, University of Oslo, Oslo, Norway** (Prof M Kalager MD PhD, Prof M Løberg MD PhD, A Macios PhD, K Garborg MD PhD, Prof Ø Holme MD PhD, Prof H-O Adami MD PhD, Prof M Bretthauer MD PhD); **Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway** (Prof M Kalager, Prof M Løberg, A Macios, K Garborg, Prof Ø Holme, Prof H-O Adami, Prof M Bretthauer); **Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway** (L Emilsson MD PhD); **Vårdcentralen Värmlands Nysäter and Centre for Clinical Research, County Council of Värmland, Värmland, Sweden** (L Emilsson); **Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden** (L Emilsson, Prof H-O Adami); **Frontier Science Scotland,**

Kingussie, UK (F Samy BSc, S Fielding PhD)**; CAUSALab, Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA, USA** (J Shi PhD, Prof M A Hernán MD PhD)**; Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA** (J Shi)**; Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam, Netherlands** (Prof E Dekker MD PhD)**; University of Amsterdam, Amsterdam, Netherlands** (Prof E Dekker)**; Department of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, Netherlands** (Prof M Spaander MD PhD)**; Research Unit, Sørlandet Hospital, Kristiansand, Norway** (Prof Ø Holme)**; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA** (A G Zauber PhD)**; Department of Epidemiology & National Cancer Registry, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland** (Prof J Didkowska MD)**; Department of Surgical Oncology, Transplant Surgery and General Surgery, Medical University of Gdansk, Gdansk, Poland** (P Spychalski MD PhD)**; Department of Research and Development, Telemark Hospital, Skien, Norway** (Prof G Hoff MD PhD)**; Cancer Registry of Norway, Norwegian Institute of Public Health, Oslo, Norway** (Prof G Hoff)

Correspondence to: Prof Michael Bretthauer, Clinical Effectiveness Research Group, University of Oslo, N-0318 Oslo, Norway
michael.bretthauer@medisin.uio.no

See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to Dec 31, 2025, for randomised controlled trials published in English that assessed the effect of colonoscopy for screening of colorectal cancer in individuals with average risk (ie, people aged ≥50 years without personal history of colorectal cancer or hereditary colorectal cancer syndrome) on colorectal cancer incidence or mortality. We used the following search terms: ("colorectal cancer" OR "colon cancer") AND ("colonoscopy") AND ("screening") AND ("mortality" OR "incidence"). Two randomised trials were identified: the SCREESCO trial in Sweden, which compares colonoscopy, faecal immunochemical testing, and no intervention; and our own trial (the NordICC trial). The SCREESCO trial has not reported results on colorectal cancer mortality or incidence yet. Our own trial reported results after 10 years of follow-up in 2022, which showed a risk of colorectal cancer at 10 years of 0·98% in the screening group and 1·20% in the no-screening group (risk ratio [RR] 0·82 [95% CI 0·70–0·93]) in intention-to-screen analyses. Colorectal cancer mortality was 0·28% in the screening group and 0·31% in the no-screening group (RR 0·90 [0·64–1·16]). The risk of death from any cause was 11·03% in the screening group and 11·04% in the no-screening group (RR 0·99 [0·96–1·04]). Some screening experts have questioned whether 10 years of follow-up was too short to observe the full benefit of colonoscopy screening. After 10-year follow-up, the analyses did not have enough statistical power to analyse important, predefined subgroups, such as women and men.

Added value of this study

We report results with longer follow-up after colonoscopy screening. Due to more colorectal cancer cases and deaths, the present report can also provide estimates for men versus women, proximal versus distal colorectal cancers, and people younger than 60 years versus 60 years and older. Finally, the report uses methodologically improved per-protocol analyses to estimate screening benefits for individuals who were actually screened, which are important for personal shared decision making.

Implications of all the available evidence

According to these new results, a single colonoscopy reduces colorectal cancer risk by 0·3% to 0·8% over 13 years. The study reveals that the risk of colorectal cancer death is significantly lower than was expected when the trial started even without screening, and that screening does not provide additional reduction of an already low risk for colorectal cancer mortality with longer follow-up than 10 years. These data might help to guide policies at the population level, where screening benefits must be weighed against other expenditures that promote public health.

comparison group of individuals who were not offered screening.[7]

It has been claimed that 10 years of follow-up is too short to fully ascertain screening benefits.[8] In this study, we report the effects of colonoscopy screening after 3 years of further follow-up in intention-to-screen and per-protocol analyses.[9] The current analysis is a priori as defined in the protocol (appendix pp 31–54). Due to substantially more colorectal cancer cases and deaths during this additional follow-up, we now also provide estimates for men and women, proximal and distal colorectal cancers, and people aged 60 years and younger versus older than 60 years.

Methods

Study design and participants

The design of the NordICC trial has been described in detail elsewhere.[6,10] Briefly, NordICC is a population-based, randomised trial comparing colonoscopy screening with no screening. Eligible individuals were men and women aged 55–64 years living in Norway, Poland, Sweden, and the Netherlands. Individuals were drawn directly from the population registries and randomly allocated (1:2) to either invitation for colonoscopy screening (screening group) or no invitation (no-screening group). Screening was done between June 8, 2009, and June 23, 2014.[6] Sex of trial participants was determined by the national identifier, which includes information on the sex of each individual in the population registries. In accordance with data protection laws in the participating countries, we did not receive information about race or ethnicity from the national registries, and we did not request this information from participants who underwent screening. Public statistics from the participating countries do not routinely report race or ethnicity but provide country of birth. According to these statistics, more than 90% of individuals in the trial recruitment areas were born in the country where they live.

As before, this analysis is based on follow-up of all 84 583 individuals in Norway, Poland, and Sweden (89·1% of all individuals originally included in the trial; appendix p 18). Data from the Netherlands were not included due to continued restrictions in availability of trial endpoints.

The study was approved by the ethical committees at all participating centres (Norway: Regional Ethics Committee of South-East Norway [2010/2187]; Poland: Maria Skłodowska Curie Memorial Cancer Center and Institute of Oncology and Medical Center for Postgraduate Education, Warsaw, Poland [30/2007]; Sweden: Swedish National Ethics Council [2007/363]; and the Netherlands: Dutch National Health Council [2009/03WBO]).[10] The study was funded by research grants in the participating countries. All authors vouch for the accuracy of the data and fidelity of the trial to the

protocol. This trial is registered with ClinicalTrials.gov, NCT00883792, and is ongoing.

Procedures

Individuals were randomly allocated to either invitation to one screening colonoscopy (screening group) or to no invitation to any screening (no-screening group).[10] Individuals randomly allocated to the screening group received a letter of invitation to screening colonoscopy. All individuals receiving the screening provided written informed consent before the colonoscopy. Individuals randomly allocated to the no-screening group did not receive any intervention and were not contacted at study enrolment. Requirement of consent was waived for individuals randomly allocated to the no-screening group by the ethical committees at all participating centres.[10]

A colonoscopy quality and training programme was implemented for the trial.[10] All lesions detected during colonoscopy were removed if feasible, and all tumours were biopsied. Dedicated histopathologists assessed all polyps and cancers according to WHO classification.[11] Participants were referred for polyp surveillance after screening following national guidelines.[6]

Poland had an opportunistic colorectal cancer screening programme in some geographical areas at trial start, but not in the area of the trial. In the other countries, no organised colorectal cancer screening of any kind was available at trial start. Colorectal cancer screening programmes using faecal immunochemical testing were gradually introduced in the participating countries region by region during follow-up. Such staggered geographical implementation of cancer screening programmes is common in Scandinavia.[12] To protect the integrity of the trial, the geographical areas in which the NordICC trial was held were not the first to start the new screening programmes and, thus, NordICC trial participants had become too old to be eligible for the screening programmes when these programmes were introduced in their geographical area. Colonoscopy screening was not available publicly or privately outside the trial.[6,10] Thus, no individuals enrolled in the trial were eligible for any colorectal cancer screening programmes outside the trial during screening or follow-up.

Outcomes

The primary outcomes were colorectal cancer incidence and mortality after 10–15 years of follow-up in intention-to-screen analyses, with first analysis after 10 years, and repeated every other year or at longer intervals (appendix pp 31–54). Secondary outcomes were colorectal cancer incidence and mortality in per-protocol analyses, all-cause mortality, subgroup analyses by age and gender, and analyses for distal and proximal colorectal cancer.

Colorectal cancer diagnosis was defined according to ICD-10 as cancer in the colon or rectum by topography codes C18 to C20, combined with ICD-O3 morphology codes for adenocarcinoma. Colorectal cancer stage was classified as early stage (Dukes A or B), late stage (Dukes C or D), or unknown. Tumours with histopathology other than adenocarcinoma were not counted as events. Proximal colorectal cancer was defined as cancers proximal for the descending colon, and distal colorectal cancer as cancers in the descending colon, sigmoid colon, or rectum. Colorectal cancer mortality was defined as colorectal cancer as cause of death registered in the cause-of-death registries in the participating countries, and a diagnosis of colorectal cancer in the national cancer registries. We followed all randomly allocated individuals by linkage to national cancer and cause-of-death registries, as previously described.[6] The sample size calculation was based on intention-to-screen analyses and has been described in detail elsewhere.[10]

Statistical analysis

Follow-up was from randomisation until date of emigration, colorectal cancer diagnosis for colorectal cancer incidence or colorectal cancer death for colorectal cancer mortality, or death or end of follow-up after 13 years, whichever came first.

To estimate the intention-to-screen effect, we calculated cumulative incidence as the 13-year risk of colorectal cancer in the screening and no-screening groups using Kaplan–Meier estimators, and colorectal cancer mortality equivalently; we compared risks using risk ratios (RRs) and risk differences, and annual colorectal cancer incidence and mortality RRs. We did analyses with and without censoring of competing events (death from causes other than colorectal cancer). As in our previous report,[6] the results were similar between these analyses (appendix p 4), and thus we focused on analyses that treated non-colorectal cancer deaths as censoring events. 95% CIs were calculated via bootstrapping. We calculated the number needed to invite to screening to prevent one colorectal cancer as the reciprocal of the 13-year risk difference of colorectal cancer incidence.

To estimate the per-protocol effect, defined as the effect of screening if all individuals randomly allocated to the screening group had been screened, we used an instrumental variable approach, which does not require measurement of all confounders to provide valid results.[9] We present estimates of per-protocol effects based on instrumental variable analyses under additive homogeneity—that is, factors that modify the effect of screening on the outcome (when estimating risk differences) do not also modify the effect of receiving an invitation on undergoing screening. The appendix (pp 7–10) also provides estimates using alternative assumptions: multiplicative homogeneity (analogous to additive homogeneity, but for RRs rather than risk differences) and monotonicity (ie, that there are no individuals who would undergo screening if not invited but would choose not to undergo screening if invited). Under a homogeneity assumption (additive or

multiplicative), the per-protocol estimate was interpreted as the effect in the entire trial population, whereas under monotonicity, the estimate was interpreted as the causal effect among those who were screened.

Role of the funding source

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

Results

Our analyses were based on 84 583 individuals from Norway, Poland and Sweden, of whom 28 217 were randomly allocated to screening and 56 366 to no screening. Participant characteristics of age, sex, and participation with screening colonoscopy in the three countries are provided in table 1. Overall, 11 841 (42·0%) of 28 217 participants invited to screening attended, varying from 6002 (33·0%) of 18 183 in Poland to 485 (39·8%) of 1219 in Sweden and 5354 (60·7%) of 8815 in Norway.[13] The median follow-up for this report was 13·0 years in both study groups (IQR 12·9–13·0, maximum 13·0). Data on adverse events and complications of the trial interventions have been reported previously.[13]

3 years of additional follow-up (from 10 years to 13 years) increased the number of colorectal cancer cases from 259 to 375 (by 45%) in the screening group and from 622 to 912 (by 47%) in the control group (table 2). Death from colorectal cancer increased from 72 to 106 (by 47%) cases in the screening group, and from 157 to 236 (by 50%) cases in the no-screening group (table 2).

The 13-year risk of colorectal cancer was 375 (1·46%) of 28 217 in the screening group and 912 (1·80%) of 56 366 in the no-screening group in intention-to-screen analyses (RR 0·81 [95% CI 0·71–0·90]; figure 1A, table 2). Figure 1A shows colorectal cancer incidence by group and figure 2 provides annual colorectal cancer incidence rate ratios. The number needed to invite for screening to prevent one colorectal cancer within 13 years was 294 (95% CI 185–588). In per-protocol analyses, colorectal cancer incidence was 1·00% in the screening group and 1·80% in the no-screening group (RR 0·55 [0·33–0·81]; table 2, figure 1B). Colorectal cancer incidence in screening participants and non-participants in the screening group compared with the no-screening group is shown in the appendix (p 20).

The 13-year risk of colorectal cancer mortality was 106 (0·41%) of 28 217 in individuals randomly allocated to screening, and 236 (0·47%) of 56 366 in those randomly allocated to no screening (RR 0·88 [95% CI 0·68–1·08]; table 2, figure 1C). The appendix (p 19) shows yearly colorectal cancer mortality rate ratios by group. In per-protocol analyses, colorectal cancer mortality was 0·33% in the screening group and 0·47% in the no-screening group (RR 0·70 [0·26–1·25]; table 2 figure 1D). Colorectal cancer mortality in screening participants and non-participants in the screening group compared with the no-screening group is shown in the appendix (p 21).

During 13 years of follow-up, 4506 (16·30%) individuals died of any cause in the invitation-to-screening group, compared with 9017 (16·34%) in the no-screening group (RR 1·00 [95% CI 0·97–1·03]; table 2).

In intention-to-screen analyses, the risk for proximal colorectal cancer was 129 (0·51%) of 28 217 in the screening

	Poland (n=54 527)	Norway (n=26 413)	Sweden (n=3643)
Group			
Attender	6002 (11·0%)	5354 (20·3%)	485 (13·3%)
Non-attender	12 181 (22·3%)	3461 (13·1%)	734 (20·1%)
Control	36 344 (66·7%)	17 598 (66·6%)	2424 (66·5%)
Sex			
Female	27 329 (50·1%)	13 194 (50·0%)	1659 (45·5%)
Male	27 198 (49·9%)	13 219 (50·0%)	1984 (54·5%)
Age at enrolment			
<60 years	28 791 (52·8%)	12 524 (47·4%)	1782 (48·9%)
≥60 years	25 736 (47·2%)	13 889 (52·6%)	1861 (51·1%)

Data are n (%). Discrepancies in numbers of analysed individuals between this analysis and the previously published 10-year follow-up study can be found in the appendix (p 28).

Table 1: **Characteristics of trial participants**

	Screening group (n=28 217)		No-screening group (n=56 366)		Risk difference, % (95% CI)	Risk ratio (95% CI)
	Number of events	13-year risk, % (95% CI)	Number of events	13-year risk, % (95% CI)		
Intention-to-screen analysis						
Colorectal cancer	375	1·46% (1·32–1·62)	912	1·80% (1·69–1·92)	−0·34% (−0·54 to −0·17)	0·81 (0·71–0·90)
Death from colorectal cancer	106	0·41% (0·34–0·50)	236	0·47% (0·42–0·54)	−0·06% (−0·16 to 0·04)	0·88 (0·68–1·08)
Death from any cause	4506	16·30% (15·87–16·74)	9017	16·34% (16·03–16·65)	−0·04% (−0·56 to 0·51)	1·00 (0·97–1·03)
Per-protocol analysis						
Colorectal cancer	..	1·00% (0·63–1·41)	..	1·80% (1·69–1·91)	−0·80% (−1·24 to −0·33)	0·55 (0·33–0·81)
Death from colorectal cancer	..	0·33% (0·13–0·55)	..	0·47% (0·42–0·53)	−0·14% (−0·37 to 0·11)	0·70 (0·26–1·25)

Table 2: **Primary and secondary endpoints in intention-to-screen and per-protocol analyses**

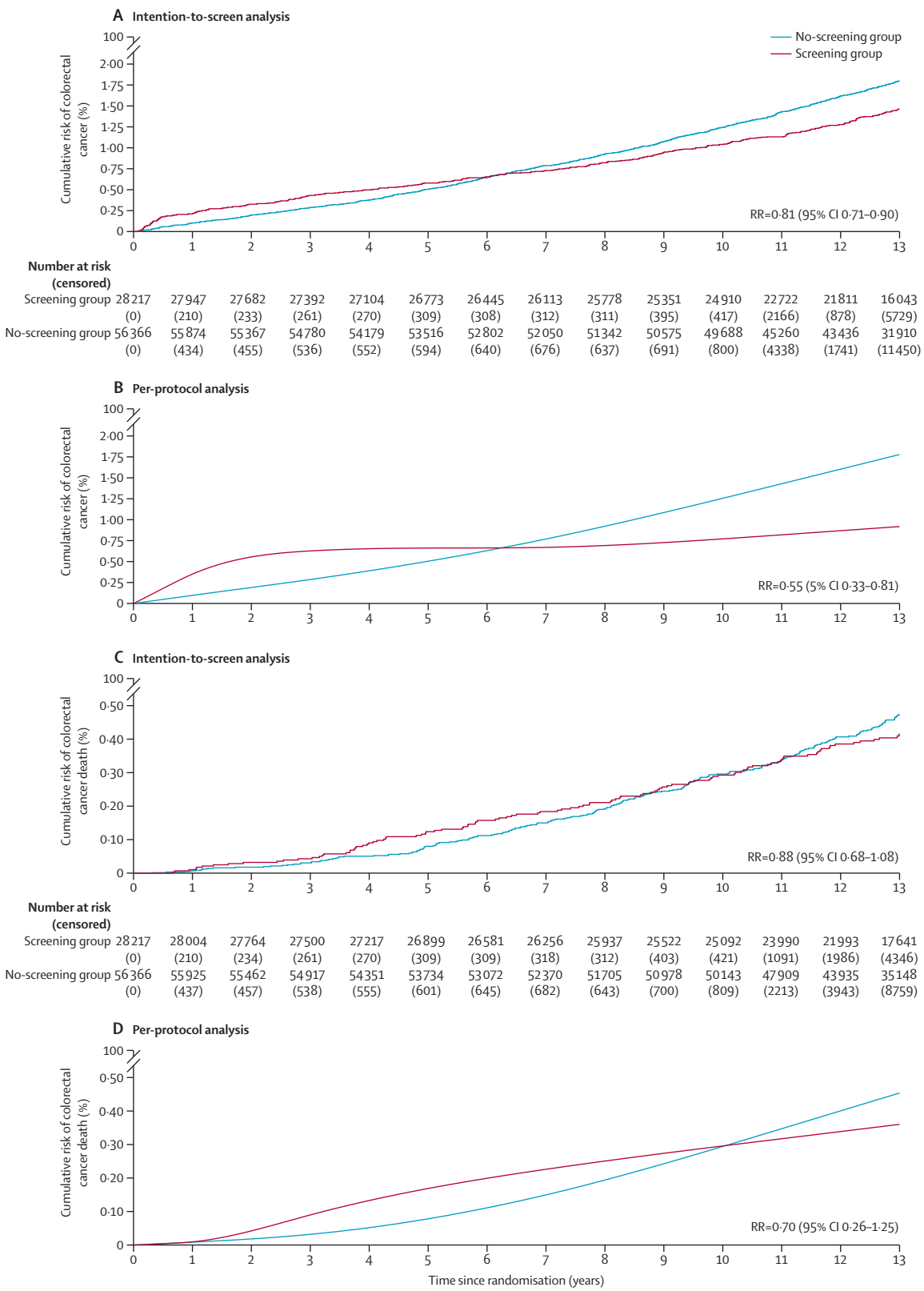

Figure 1: **Cumulative colorectal cancer incidence and mortality at 13 years in intention-to-screen and per-protocol analyses**
Colorectal cancer incidence in intention-to-screen analysis (A) and per-protocol analysis (B). Colorectal cancer death in intention-to-screen analysis (C) and per-protocol analysis (D). Risk curves based on per-protocol estimations were smoothed with restricted cubic splines with knots at 0·5, 1, 3, 7, and 11 years of follow-up. RR=risk ratio.

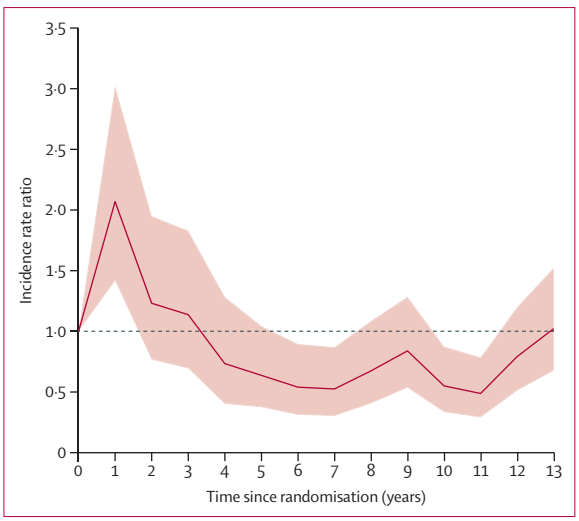

Figure 2: **Yearly rate ratios for colorectal cancer incidence in the screening group compared with the no-screening group, intention-to-screen analysis**
Shading indicates 95% CIs. The dotted line indicates similar incidence rate ratio in the two groups.

group and 283 (0·56%) of 56 366 in the no-screening group (RR 0·91 [95% CI 0·71–1·09]), and the risk for distal colorectal cancer was 224 (0·87%) in the screening group and 563 (1·11%) in the no-screening group (RR 0·79 [0·65–0·89], interaction p<0·0001; figure 3A, B, appendix pp 5–6).

In intention-to-screen analyses, the risk for death due to proximal colorectal cancer was 33 (0·13%) of 28 217 in the screening group and 67 (0·13%) of 56 366 in the no-screening group (RR 0·95 [95% CI 0·56–1·35]), and the risk for death due to distal colorectal cancer was 68 (0·27%) in the screening group and 154 (0·31%) in the no-screening group (RR 0·87 [0·62–1·12]; appendix pp 5–6). Cumulative colorectal cancer mortality according to cancer location is shown in the appendix (p 22). Per-protocol estimates for proximal versus distal colorectal cancer are provided in the appendix (pp 7–10).

In men, the 13-year colorectal cancer risk was 214 (1·69%) of 14 154 in the screening group and 541 (2·19%) of 28 247 in the no-screening group in intention-to-screen analyses (RR 0·77 [95% CI 0·64–0·88]), whereas the corresponding risks were 161 (1·24%) of 14 063 versus 371 (1·43%) of 28 119 in women (RR 0·87 [0·70–1·02], interaction p<0·0001; figure 3C, D). Cumulative colorectal cancer mortality according to sex is provided in the appendix (p 23).

Participants aged 55–59 years at enrolment in the trial had a 13-year colorectal cancer risk of 167 (1·26%) of 14 367 in the screening group in intention-to-screen analyses, compared with 362 (1·38%) of 28 730 in the no-screening group (RR 0·91 [95% CI 0·74–1·07]) The corresponding rates were 208 (1·68%) of 13 850 and 550 (2·25%) of 27 636 in participants aged 60–64 years at enrolment in intention-to-screen analyses (RR 0·75 [0·62–0·85]). The appendix shows cumulative colorectal cancer incidence (p 24) and mortality (p 25) according to age group, a forest plot of colorectal cancer incidence in subgroups (p 27), and per-protocol estimates for subgroup analyses (pp 7–10).

Colorectal cancer stages in screening and no-screening groups based on Duke's stage are provided in the appendix (pp 7–10).

61 participants included in this report were diagnosed with colorectal cancer at screening. Of these, 47 were distal cancers and 12 had a proximal location (two had an unclassified location). In screening participants, 65 colorectal cancers (27 distal and 32 proximal location, and six unclassified location) were diagnosed after screening over the course of the 13-year follow-up, for a risk of cancer after colonoscopy in screening participants of 65 (0·55%) of 11 841.

Sensitivity analyses gave per-protocol estimates using alternative assumptions (multiplicative homogeneity and monotonicity; appendix p 11) and per-protocol estimates with deaths from causes other than colorectal cancer not treated as censoring events (appendix p 12). Country-specific analyses for Poland and Norway for colorectal cancer incidence and mortality in intention-to-screening and per-protocol analyses are given in the appendix (pp 16–17).

Discussion

After 13 years of follow-up, the relative colorectal cancer incidence reduction was 19% (compared with 18% at 10 years) and the absolute risk reduction was 0·34 percentage points (compared with 0·20 at 10 years) for screening versus no screening in intention-to-screen analyses. The corresponding relative colorectal cancer mortality reduction was 12% and the absolute risk reduction 0·06 percentage points, but these estimates were not statistically significant.

Due to the almost 50% greater number of events in the extended follow-up, we could more precisely establish colonoscopy benefits in the distal versus proximal colon, for people younger than 60 years versus 60 years and older, and for men versus women. Our data suggest that colonoscopy reduces colorectal cancer incidence in the distal colon by 21% in intention-to-screen analyses (appendix pp 5–6), whereas effect estimates are smaller and imprecise in the proximal colon. As expected, colorectal cancer risk was larger in men than in women in both study groups. Colonoscopy could be more effective in men than in women, but the differences are not statistically significant (appendix pp 5–6).

We did not observe a clinically relevant cancer stage shift (detecting cancers earlier in the screening group) between the screening and no-screening groups (appendix p 11). This finding is not surprising because stage shift of cancer due to screening applies only to cancers detected at screening (or surveillance after

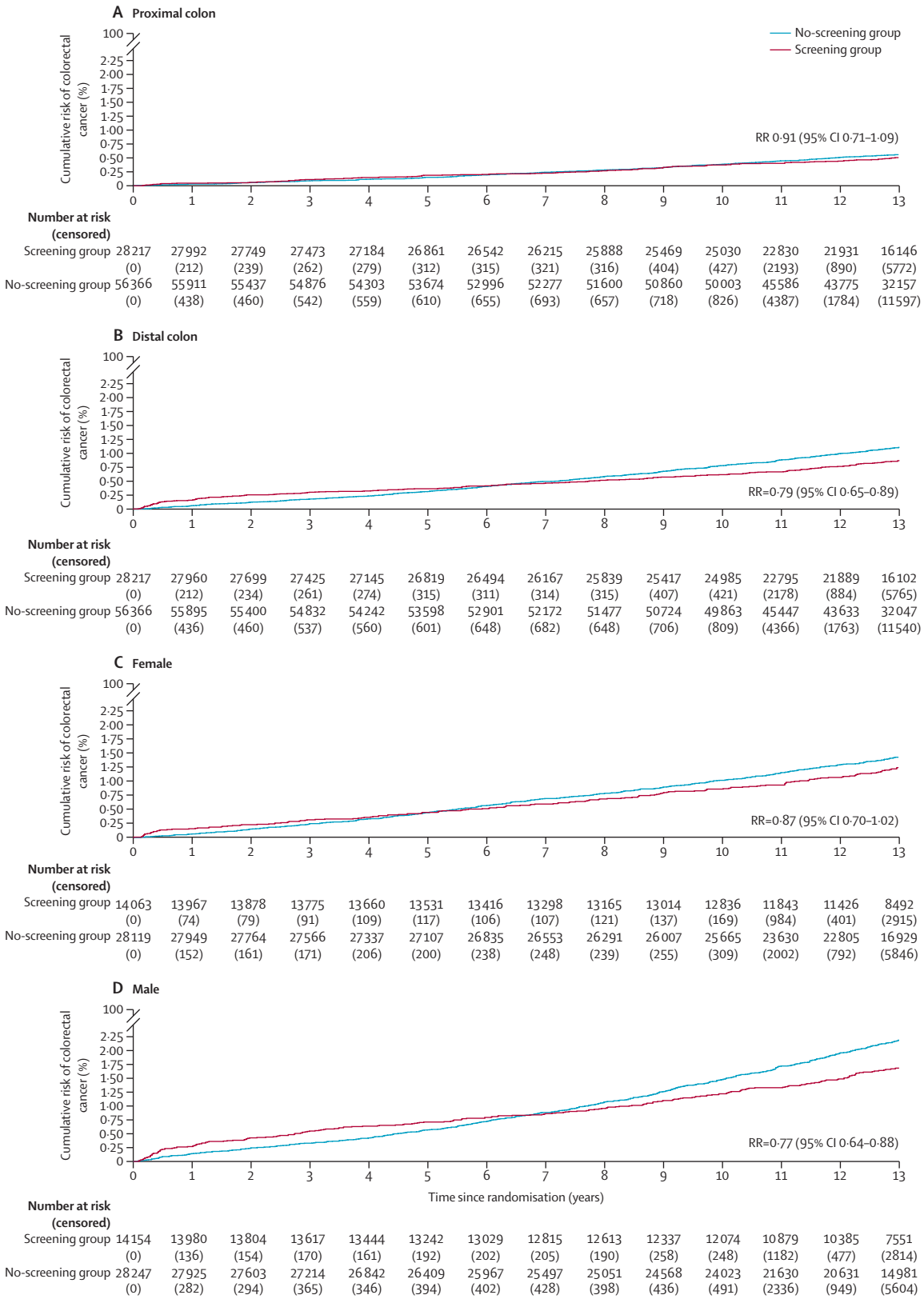

Figure 3: **Cumulative colorectal cancer incidence at 13 years in intention-to-screen analysis according to cancer location and sex**
Proximal colorectal cancer incidence* (A), distal colorectal cancer incidence* (B), colorectal cancer incidence in female participants (C), and colorectal cancer incidence in male participants (D). *Proximal colorectal cancer: location proximal for the descending colon. Distal colorectal cancer: location in the descending colon, sigmoid colon, or rectum.

screening); at 13-year follow-up, screening-detected colorectal cancer only amounted to 60 (16%) of 375 colorectal cancers in the screening group. Cancers detected later were due to clinical symptoms, as there was no colonoscopy screening outside of the trial and screening was only offered once.

Our risk estimates were determined by the causal effect of colonoscopy and the participation rates among individuals invited to screening. Because overall participation with screening was only 42%, the results from our per-protocol analyses are important for clinical decision making. Whereas previous per-protocol estimates might have been less reliable due to restricted access to data on risk factors that predict participation to the intervention, the per-protocol effect estimates in this report use instrumental variable methodology, which is not dependent on the availability of such data.[9] Using this approach and three different assumptions regarding effect homogeneity and monotonicity, colonoscopy screening reduced colorectal cancer incidence by 0·8 percentage points (from about 1·8 to 1·0, depending on assumptions), a 45% relative risk reduction (table 2), assuming that all people would participate in screening. However, the per-protocol effect estimates of screening benefit on colorectal cancer mortality are still imprecise.

Colonoscopy as applied in our trial and in most colorectal cancer screening programmes around the world is mainly a preventive screening test; its primary target is to detect and remove benign polyps to prevent them from growing into cancer. Thus, the primary potential benefit of colonoscopy screening is reduction in colorectal cancer incidence. Because only people who get colorectal cancer can die from colorectal cancer, colonoscopy will also reduce colorectal cancer mortality if it reduces colorectal cancer incidence, provided that there are no changes in colorectal cancer treatment that would alter prognosis of individuals with colorectal cancer. However, prognosis of colorectal cancer has improved dramatically due to advances in chemotherapy, surgery, and radiotherapy, and the advent of immune therapy. Since we planned the trial almost 20 years ago, colorectal cancer has evolved from a disease with high mortality to a chronic disease that most individuals survive.[1] The observed colorectal cancer incidence in the non-screening group (1·80%) is similar to the predicted rate when we planned the trial (1·85%), whereas the observed colorectal cancer mortality in the non-screening group (0·47%) is half of what it was when we planned the trial (0·82%; appendix pp 15, 26). This finding might also explain the smaller absolute benefit for colorectal cancer mortality in our trial than in the sigmoidoscopy trials that took place about 10–15 years before our trial, when colorectal cancer mortality was higher.[14,15] Although a reduction in colorectal cancer incidence without a subsequent decline in colorectal cancer mortality seems biologically implausible, it is uncertain whether longer follow-up will be able to document a statistically significant reduction in colorectal cancer mortality and, given the very low risk, it seems questionable whether such an effect would be clinically relevant (appendix p 15).

Quality of colonoscopy performance is associated with colorectal cancer risk after screening. The risk of colorectal cancer for screening participants at this time of follow-up is 65 (0·55%) cancers in 11 841 participants. This risk corresponds well with the risk in a recent nationwide analysis of the Polish screening programme, which reported a 10-year risk of cancer after colonoscopy of 0·38% for all participants, and 0·32% in participants screened by physicians with an adenoma detection rate of 26% or above.[16] With 3 years longer follow-up in our trial compared with the Polish report, and thus higher risk, the present interval cancer estimates confirm a high quality of colonoscopies performed in the NordICC trial.

Strengths of our trial are its randomised design and large size, its population of screening-naive participants, the minimal screening contamination of the control group, and the complete, long-term follow-up of all randomly allocated individuals. Limitations include the participation rate of 42% (which was expected when planning the trial) and the absence of individual data on colonoscopies after screening. Differences in ascertainment of colorectal cancer mortality between the study groups are unlikely, firstly because the intervention (invitation to colonoscopy) happened several years before death for most participants (appendix p 21), and secondly because we did not involve general practitioners (who often fill in death certificates for their patients) in the study procedures. Thus, general practitioners were not involved in decision making about trial participation or follow-up, which diminishes ascertainment bias for cause of death. Finally, we cannot rule out that some individuals in the control group have been screened for colorectal cancer on their own initiative outside any organised screening, although we believe this number to be negligible, because we were able to track background colonoscopy activity through national registries in Norway and Poland (the two countries with the highest contributions of participants in the trial) and did not observe increased activity.[17]

Continued follow-up of the NordICC trial remains important to document more definitively whether a mortality reduction is achievable by colonoscopy screening. Longer follow-up of our trial will also investigate the duration of a preventive effect of one colonoscopy on colorectal cancer incidence. This follow-up is important to tailor screening programmes regarding repetition of screening tests, a major driver of costs and resources. A recent randomised trial in Spain reported similar performance of biennial faecal immunochemical testing and one colonoscopy in intention-to-screen analyses.[7] However, participation with screening was significantly lower in both screening groups in the Spanish trial compared with our trial. Per-protocol analyses in the Spanish trial indicated lower

colorectal cancer incidence in those screened with colonoscopy than those who underwent faecal testing, but the analyses were not performed with causal inference methodologies.

In summary, a single colonoscopy reduces colorectal cancer risk by 0·3–0·8% during a follow-up of 13 years. The risk of colorectal cancer death is very low even without screening, and the hope of finding a screening benefit on colorectal cancer mortality with longer follow-up is so far not substantiated.[8] We encourage the screening community to consider what is most important for a preventive screening test such as colonoscopy. Screening might be justified if it prevents people from getting cancer even without reducing the risk of dying. On the population level, screening benefits must be weighed against other expenditures that promote public health.

Contributors

MFK, H-OA, GH, JR, AGZ, MK, ML, and MB were involved in conception and trial design. KG, ØH, GH, MFK, JR, MS, ED, and MR were involved in trial interventions. MFK, MB, AM, and GH accessed and verified the data. AM, FS, SF, JS, and MAH provided statistical expertise. MFK, MB, and H-OA were involved in drafting this manuscript. All authors provided critical revision of the manuscript and intellectual content, had full access to all of the data in the study, and were responsible for the final decision to submit for publication.

Declaration of interests

MB reports research funding from the Norwegian Research Council and the Health Fund of South-East Norway. FS and SF report research funding from Oslo University Hospital. MFK reports honoraria for speaking and teaching from Fujifilm; and consulting fees from Olympus. MAH reports grants and contracts from the US National Institutes of Health, the US Department of Veterans Affairs, and Novo Nordisk; consulting fees from ProPublica; participation on an advisory board for Adia; and stock options in Adigens Health. ED reports consulting fees from Olympus, Fujifilm, Norgine, Exact Sciences, and ProMedCS; honoraria from Olympus, Norgine, Ipsen (Mayoly), Fujifilm, Steris, and Pentax; leadership or fiduciary roles in CRC Screening; committee roles for the World Endoscopy Organization and the national colorectal cancer screening programme of the Netherlands; guideline commissions, position statements, etc for the European Society of Gastrointestinal Endoscopy and the European Hereditary Tumour Group; and endoscopic equipment from Fujifilm. All other authors declare no competing interests.

Data sharing

Individual participant data, including data dictionaries, can be shared upon request to the NordICC trial steering committee stating the purpose and nature of the intended use, provided that the requesting party has approval for the intended use from the ethics committees that approved the trial. The study protocol, including the statistical analysis plan, is available from the trial principal investigator (MB) on request.

Acknowledgments

This study was funded by the Nordic Cancer Union, the Norwegian Cancer Society, the Norwegian Research Council (197309), and the Health Fund of South-East Norway (5135). Dr Falk Pharma (Freiburg, Germany) provided the bowel preparation free of charge for colonoscopies in Norway. This study also benefited from grant support from the National Centre for Research and Development of Poland (N R13 0024 04), the Polish–Norwegian Research Programme (Pol-Nor/204233/30/2013), the Medical Center for Postgraduate Education (501-1-09-12-12/22), the Polish Foundation of Gastroenterology, the Dutch Ministry of Health and Health Care Prevention Program–Implementation (ZonMw 2008), the Netherlands Organisation for Health Research and Development of the Dutch Ministry of Health (ZonMw 120720012), the Centre for Translational Molecular Medicine (CTMM DeCoDe-project), the Swedish Cancer Foundation (2010/345 and CAN 2013/553), Regional Forskningsfond i Uppsala-Örebro Regionen, a Karolinska Institutet Distinguished Professor Award to H-OA (2368/10–221), and AFA (130072). We would like to thank research coordinator Siv Isaksen for help with registry data access and monitoring.

References

1 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; **74:** 229–63.
2 Helsingen LM, Kalager M. Colorectal cancer screening—approach, evidence, and future directions. *N Engl J Med Evid* 2022; **1:** EVIDra2100035.
3 Lauby-Secretan B, Vilahur N, Bianchini F, et al. International Agency for Research on Cancer Handbook Working Group. The IARC perspective on colorectal cancer screening. *N Engl J Med* 2018; **378:** 1734–40.
4 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.
5 Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal cancer screening. An updated modeling study for the US Preventive Services Task Force. *JAMA* 2021; **325:** 1998–2011.
6 Bretthauer M, Løberg M, Wieszczy P, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med* 2022; **387:** 1547–56.
7 Castells A, Quintero E, Bujanda L, et al. Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial. *Lancet* 2025; **405:** 1231–39.
8 Dominitz JA, Robertson DJ. Understanding the results of a randomized trial of screening colonoscopy. *N Engl J Med* 2022; **387:** 1609–11.
9 Shi J, Løberg M, Kalager M, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death: instrumental variable estimation of per-protocol effects. *Eur J Epidemiol* 2025; **40:** 419–25.
10 Kaminski MF, Bretthauer M, Zauber A, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. *Endoscopy* 2012; **44:** 695–702.
11 Hamilton SR, Aaltonen LA (eds). World Health Organization classification of tumors: pathology and genetics of tumors of the digestive tract. Lyon: IARC Press, 2000: 104–19.
12 Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med* 2010; **363:** 1203–10.
13 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.
14 Holme Ø, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomized trials. *BMJ* 2017; **356:** i6673.
15 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.
16 Pilonis ND, Spychalski P, Kalager M, et al. Adenoma detection rates by physicians and subsequent colorectal cancer risk. *JAMA* 2025; **333:** 400–07.
17 Bretthauer M, Løberg M, Kaminski MF. Colonoscopy screening and colorectal cancer incidence and mortality. *N Engl J Med* 2023; **388:** 376–79.