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ORIGINAL RESEARCH

Accounting for differential exclusions in the Nordic-European initiative on colorectal cancer trial discloses stronger-than-reported effects of screening colonoscopy

Hermann Brenner[a,b,*], Tim Holland-Letz[c], Michael Hoffmeister[a], Thomas Heisser[a]

[a]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
[b]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
[c]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

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Abstract

Objectives: Recently, results on colorectal cancer (CRC) incidence and mortality reduction by the offer of screening colonoscopy were reported for the first time from a randomized controlled trial (RCT), the Nordic-European Initiative on Colorectal Cancer (NordICC) trial. Despite randomization, there was a substantially lower proportion of postrandomization exclusions of CRC cases due to cancer registry-recorded date of diagnosis before recruitment in the invited group than in the usual-care group. We aimed to evaluate the impact of such differential exclusions on the trial's effect estimates on CRC risk.

Study Design and Setting: We compared reported postrandomization exclusions of CRC cases due to cancer registry-recorded date of diagnosis, and we derived adjusted effect estimates on CRC risk accounting for the reported differential postrandomization exclusion of CRC cases in the invited group and the usual-care group.

Results: Reported postrandomization exclusion proportions of CRC cases were originally reported as 52/31,472 (0.17%) and 159/63,133 (0.25%) in the invited and usual-care group, respectively, ($P < .005$) in an analysis, including participants from all four NordICCstudy countries and as 52/28,277 (0.20%) and 164/56,529 (0.29%) in the recent analysis of 10-year follow-up data from three of the countries ($P = .018$). Accounting for the differential exclusion proportions increased the estimated CRC risk reduction (95% CI) from originally reported 18% (7%−30%) to 25% (95% CI 13%−35%) in intention-to-screen analysis. Estimated reduction of CRC risk among screening attenders increased from originally reported 31% (17%−45%) to 50% (25%−69%) in adjusted per-protocol analysis.

Conclusion: Accounting for differential postrandomization exclusions of CRC cases leads to stronger-than-reported effect estimates in the so far only RCT on long-term effects of screening colonoscopy.

Keywords: Colonoscopy; Colorectal cancer; Prevention; Randomized trial; Risk; Screening

1. Background

Based on intriguing evidence from observational studies [1,2], screening colonoscopy has been recommended for lowering colorectal cancer (CRC) incidence and mortality by expert panels and national and international guidelines [3,4]. In the United States, where screening colonoscopy has been used by the majority of older adults in recent decades, CRC incidence and mortality have approximately halved [5,6], despite unfavourable trends in the prevalence of CRC risk factors and an increase of CRC incidence at younger, prescreening ages [7].

Only very recently, first results on the effects of screening colonoscopy on CRC incidence and mortality became available from a randomized controlled trial (RCT), the Nordic-European Initiative on Colorectal Cancer (NordICC) trial [8]. In this pragmatic trial, participants were directly identified through population registries in four Northern European countries. Although the NordICC trial showed a significant reduction in CRC risk, reported

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* Corresponding author. Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), INF 280, 69120 Heidelberg, Germany.
E-mail address: h.brenner@dkfz.de (H. Brenner).

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What is new?

Key findings

- We assessed and compared postrandomization exclusions in the invited group and the usual-care group in the Nordic-European Initiative on Colorectal Cancer (NordICC) trial, the first randomized trial reporting on long-term effects of screening colonoscopy on colorectal cancer (CRC) incidence and mortality.
- Despite randomization, there were statistically significant, non-negligible differences in proportions of postrandomization exclusions between both groups.

What this adds to what was known?

- Our study illustrates a major source of bias and an approach to account for this bias in the analysis of this pragmatic randomized trial.
- Our analyses demonstrate that effects of screening colonoscopy are likely to be substantially stronger than suggested by published results of the NordICC trial.

What is the implication and what should change now?

- Future design, conduct, and analyses of pragmatic randomized trials like the NordICC trial should take utmost care to avoid or at least minimize the type of bias disclosed in this article.

preventive effects were weaker than anticipated, raising concerns that screening colonoscopy might be less effective than previously thought [9,10].

However, another intriguing but not further discussed observation in the NordICC study publication was a substantially lower proportion of postrandomization exclusions of CRC cases in the group invited for screening than in the usual-care group. Such exclusions were made for cancers diagnosed before randomization, which became known by the record linkage with updated cancer registry databases only after randomization. The differential exclusion proportions appear surprising on first view, because randomization should have ensured equal proportions of people with a history of previous CRC in both groups.

Regardless of their origin, differential exclusion proportions after randomization challenge the main asset of randomized trials, and it appears mandatory to account for such differences in the analysis. In this article, we aimed to assess by how much violation of comparability resulting from differential exclusion proportions in the invited group and the usual-care group may have affected the observed results of the NordICC trial, and to derive effect estimates on CRC risk after accounting for the differential exclusions.

2. Methods

2.1. Study design and data sources

Our analyses are based on published data from the NordICC trial [8,11]. Details on the NordICC trial design and main results have been reported previously [8,11,12]. Briefly, from 2009 to 2014, men and women aged 55−64 years were drawn from population registries in Poland, Norway, Sweden, and the Netherlands and randomly allocated in a 1:2 ratio to either receive an invitation for a single-screening colonoscopy (intervention group) or to usual-care (control group). In this pragmatic trial, only 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. Men and women 55−64 years of age who had not previously undergone screening were eligible for participation. The exclusion criteria were death or the diagnosis of CRC before trial entry, as assessed in national registries before randomization [11,12]. Death or the diagnosis or CRC before randomization that became known after randomization only, for example, by record linkage with updated cancer registry databases, led to postrandomization exclusions.

First results on CRC incidence and mortality were reported after a median follow-up of 10 years in October 2022 [8]. This report was based on 84,585 participants from Poland, Norway, and Sweden (n = 54,528, 26,411, and 3,646, respectively; participants from the Netherlands could not be included in that analysis due to confidentiality issues). Of the 84,585 finally included participants, 28,220 were assigned to the intervention group and 56,365 participants were assigned to the usual-care group. The screening offer was used by 11,843 participants (42%) in the intervention group. Follow-up with respect to CRC incidence and mortality was again conducted by record linkage with cancer registries and cause-of-death registries in all three countries.

The study was approved by the ethics committees of all participating centers, the Swedish National Council on Medical Ethics, and the Health Council of the Netherlands.

2.2. Statistical analyses

We first provide an overview of data on postrandomization exclusions due to deaths and previous CRC diagnoses before inclusion, which were extracted from flow diagrams presented in previous NordICC publications [8,11]. We compared the proportions of exclusions due to these criteria between the invited group and the usual-care group by chi-squared tests (two-sided testing at an alpha level of 0.05).

Given the substantially lower postrandomization exclusion proportion of CRC cases with the date of diagnosis before randomization in the invited group than in the usual-care group despite the random assignment, we carried out a reanalysis of the trial results, assuming the same exclusion proportion of participants due to a prerandomization diagnosis of CRC in the invited group as in the usual-care group. We determined the number of missing postrandomization exclusions due to prerandomization CRC diagnoses in the invited group, as the difference between the observed number of such exclusions and the expected number, if the exclusion proportion had been the same as in the usual-care group.

We carried out a reanalysis of the published data after adding the presumably missed exclusions to the reported exclusions in the invited group, which is equivalent to subtracting the number of missed exclusions of prerandomization diagnoses from the reported number of CRC cases in the invited group. More specifically, the number of missed exclusions was subtracted from the reported number of CRC cases in the screened group. The rationale for the ''allocation'' of the missed exclusions to screening participants is that all follow-up procedures with respect to identification of CRC cases by record linkage with cancer registries should have been exactly identical among nonattenders and participants in the usual-care group, whereas direct contact with the participants and screening-related activities may have had an impact on recorded dates of cancer diagnosis in cancer registries.

We derived both intention-to-screen and per-protocol estimates of screening effects on CRC risk, both without and with adjustment for missed exclusions among screening attenders. Intention-to-screen estimates quantify the impact of the screening offer on CRC risk; per-protocol estimates quantify the impact of actual use of CRC screening. Screening effects were expressed by CRC risk ratios and their 95% confidence intervals.

Because ''crude'' per-protocol estimates comparing risk among screening users with the risk in the usual-care group may be biased by selective use of screening by participants with higher or lower CRC risk, we adopted an analytical approach suggested by Cuzick et al [13] for estimating the magnitude of a treatment effect among compliers, which is asymptotically unbiased and respects the randomization. Following this approach, we estimated the number of prevented CRC cases in the invited group, denoted P_{cases}, as the difference between expected CRC cases in the absence of screening effects and observed cases. It is worth noting that this difference is not affected by the potentially selective use of screening. Assuming that screening could only have prevented CRC cases among those who used it, we obtained unbiased adjusted per-protocol effects of screening by comparing the observed numbers of CRC cases among screening attenders, denoted O_{cases}, and the sums of these and the prevented cases, and we expressed these effects as adjusted per-protocol risk ratios, that is, as $O_{cases}/(O_{cases} + P_{cases})$. We calculated 95% confidence intervals for the adjusted effect estimates as the 2.5th and 97.5th percentile of 1 million runs of Monte Carlo simulations of the NordICC trial using the observed case proportions (including the proportions of excluded participants due to prerandomization CRC diagnoses) as expected values for each simulation run.

In addition to the calculations on CRC risk reduction in relative terms, we carried out analogous calculations to assess the impact of differential exclusions on estimates of absolute risk reduction and of the number of participants needed to invite to prevent one CRC case.

3. Results

Table 1 shows earlier reported [11] and updated [8] postrandomization exclusions due to death or CRC diagnosis before randomization. In agreement with expectations from the randomized design, no differences were seen in postrandomization exclusion proportions of deaths between the invited group and the usual-care group. By contrast, the postrandomization exclusion proportion due to prerandomization CRC diagnoses was significantly lower in the invited group, both in the earlier analysis [11], including all four countries (0.17% vs. 0.25%, relative exclusion proportion 0.66, $P = .005$), and in the later analysis, based on updated cancer registry data [8] in which first results on CRC risk and deaths were reported (0.20% vs. 0.29%, relative exclusion proportion 0.69, $P = .018$).

If the exclusion proportion due to prerandomization CRC diagnoses in the invited group had been the same as in the usual-care group, as expected due to the randomization, there should have been $282{,}77 \times (164/56{,}529) = 82$ such exclusions in the invited group in the final analysis. However, only 57 exclusions were observed in this group, suggesting that $82-57 = 25$ exclusions might have been missed. As case ascertainment procedures were exactly the same in screening nonattenders and the usual-care group, but different in screening attenders, it is plausible to assume that the 25 missed exclusions occurred among screening attenders, for example, by the updates of previously recorded prerandomization dates of diagnosis in the cancer registries after histological confirmation of CRCs at screening colonoscopy.

Table 2 shows the count data of the NordICC trial and derived risk ratios on CRC risk before and after accounting for differential exclusions. Not accounting for differential exclusions, risk ratios (95% CI) of 0.83 (0.72−0.96) and 0.66 (95% CI 0.49−0.90) for the risk of CRC diagnosis were derived in intention-to-screen and adjusted per-protocol analyses, respectively. These results are very close

Table 1. Postrandomization exclusions in NordICC trial and derived relative exclusion proportions

Reference	Randomization and exclusions	Invited group	Usual-care group	*P* value
Bretthauer et al 2016 (12)[a]	Randomized	31,589	63,370	
	Excluded: Prerandomization death	117 (0.37%)	237 (0.37%)	
	Relative exclusion proportion (95% CI)	0.99 (0.79–1.24)		.931
	Randomized and alive	31,472	63,133	
	Excluded: Prerandomization CRC	52 (0.17%)	159 (0.25%)	
	Relative exclusion proportion (95% CI)	**0.66 (0.48–0.90)**		**.005**
Bretthauer et al 2022 [8]	Randomized	28,395	56,784	
	Excluded: Prerandomization death	118 (0.42%)	255 (0.45%)	
	Relative exclusion proportion (95% CI)	0.93 (0.74–1.15)		.487
	Randomized and alive	28,277	56,529	
	Excluded: Prerandomization CRC	57 (0.20%)	164 (0.29%)	
	Relative exclusion proportion (95% CI)	**0.69 (0.51–0.94)**		**.018**

CI, confidence interval; CRC, colorectal cancer.
Statistically significant differences ($P < .05$) between the invited group and the usual-care group are marked in bold.
[a] Original report of exclusions for participants from all four countries contributing to the NordICC trial (Poland, Norway, The Netherlands, Sweden).

to the corresponding risk ratios reported by Bretthauer et al [8], which were based on person-time rather than count data (intention-to-screen and adjusted per-protocol risk ratios, using Cuzick et al type of adjustment: 0.82, 95% CI: 0.70–0.93 and 0.66, 95% CI: 0.46–0.86, respectively).

After accounting for differential exclusions, stronger effect estimates were obtained. In particular, the risk ratios (95% CIs) for CRC diagnoses in the intention-to-screen analysis changed from 0.83 (0.72–0.96) to 0.75 (0.65–0.87), suggesting 25% rather than 17% risk reduction. Similarly, the risk ratio (95% CI) for the adjusted per-protocol estimate changed from 0.66 (0.49–0.90) to 0.50 (0.31–0.75), suggesting that users of screening colonoscopy reduced their risk by 50% rather than 34%.

As Table 3 shows, accounting for differential exclusions would increase the reported difference in 10-year cumulative risk from 0.22% to 0.31% and reduce the number of people needed to invite to prevent one CRC case from 455 to 323.

4. Discussion

In this article, we examined proportions of participants who were excluded from the NordICC trial after randomization due to a previous CRC diagnosis and found them to be substantially and statistically significantly lower in the invited group than in the usual-care group, despite the

Table 2. Count data of the NordICC trial and derived risk ratios before and after accounting for differential exclusions

Accounting for differential exclusions	Group/Analysis	Invited group			Usual-care group
		Screening attenders	Nonattenders	Total	
No	Participants [N]	11,843	16,377	28,220	56,365
	CRC cases [N]	102	157	259	622
	Risk ratio (95% CI)				
	Intention-to-screen	0.83 (0.72–0.96)			
	Adjusted per-protocol	0.66 (0.49–0.90)			
Yes	Participants [N]	11,843–25 = 11,818	16,377	28,220–25 = 28,195	56,365
	CRC cases [N]	102–25 = 77	157	259–25 = 234	622
	Risk ratio (95% CI)				
	Intention-to-screen	0.75 (0.65–0.87)			
	Adjusted per-protocol	0.50 (0.31–0.75)			

CI, confidence interval; CRC, colorectal cancer.

Table 3. Cumulative 10-year risk data of the NordICC trial and derived risk differences and numbers needed to invite to prevent one CRC before and after accounting for differential exclusions

Metric	Invited group	Usual-care group	Difference	Number needed to invite
Reported CRC risk (8)	0.98%	1.20%	0.22%	1/0.22% = 455
Postrandomization exclusions of CRC	0.20%	0.29%	0.09%	
Adjusted CRC risk[a]	0.89%	1.20%	0.31%	1/0.31% = 323

CRC, colorectal cancer.

[a] 0.98%−0.09% (adjusted for differential exclusions of prerandomization CRC between invited group and usual-care group despite randomization).

randomization. We furthermore derived estimates of CRC risk reduction that account for the differential exclusion proportions in the invited group and the usual-care group. Our analyses yield effect estimates that are stronger and more in line with an extensive body of evidence from individual-level and population-level epidemiological studies [2,14−16] than the reported ones.

Identification of eligible participants without a previous CRC diagnosis and follow-up of participants with respect to CRC incidence in the NordICC trial was performed by record linkage with cancer registries. This is a rational, efficient, and economic approach for such a large trial, including close to 100,000 participants. However, this approach also goes along with specific limitations related to completeness, accuracy, and timeliness of cancer registration, which require careful consideration in the design, conduct, and interpretation of such a registry-based trial. For example, complete registration of all cases is commonly achieved with a substantial delay by population-based cancer registries [17,18]. The median time from incidence to registration of CRC cases has been estimated to be around 600 days from 2010 to 2014 in population-based cancer registries in European countries [19]. Therefore, postrandomization exclusion of participants whose prior cancer diagnosis became known only after randomization, as performed by the NordICC study group, is compulsory because there is no way screening could have affected diagnosis or occurrence of such cases. It is of paramount importance, however, that such exclusions are made in a comparable manner in the invited group and the usual-care group. Given that this was aimed for by randomization and equal record linkage procedures in both study arms, it appears surprising on first view that the number of postrandomization exclusions due to a previous cancer diagnosis was significantly lower, by approximately one-third, in the invited group than in the usual-care group. Such discrepancy despite randomization raises concerns about comparability of exclusions of CRC cases and their potential impact on effect estimates.

Although the NordICC trial publications do not address potential reasons for the differential exclusion proportions, there appear to be a number of plausible mechanisms that might have contributed to such differential exclusions. For example, CRC cases were reported to have been detected at screening colonoscopy among 62 screening participants. It is conceivable that some proportion of these participants had previous contacts with the medical system that might have led to a preliminary or suspected but not finally histologically confirmed CRC diagnosis that was reported to the cancer registry. The invitation to screening colonoscopy may even have triggered screening attendance and final diagnosis among people with symptoms or suspicion of CRC. In such cases, histological confirmation of CRC following screening colonoscopy might have led to an updated date of diagnosis in the cancer registry records according to established cancer registration rules [20], thereby preventing exclusion due to the original prerandomization diagnosis. Even though postrandomization histological verification of preliminary prerandomization CRC diagnoses may also have reduced the number of identified exclusions in the usual-care group and among screening nonattenders to some extent, such reductions may have been less comprehensive than in screening attenders who underwent colonoscopy shortly after randomization. A more common shift of date of diagnosis among participants with screening detected cancers may explain some of the significantly lower rate of exclusions due to a previous CRC diagnosis in the screening group, and, more specifically, among screening attenders. It is worth noting, however, that this is just one example of potential underlying mechanisms, and that the differential postrandomization exclusions would have led to underestimation of screening effects and stronger effect estimates after accounting for differential exclusion proportions regardless of the reasons for the differential exclusions. Even if CRC cases shortly before randomization had truly occurred less commonly in the invited group than in the usual-care group simply by chance (despite the very low *P* value for the comparison of exclusion proportions), this should have gone along with an apparent ‘‘compensatory’’ excess occurrence of CRC cases shortly after randomization in the invited group, as overall, the risk of CRC in the absence of the screening offer should have been identical in the invited group and the usual-care group due to randomization. Our approach would equally correct for such an imbalance, which would have nothing to do with true screening effects.

When looking at the patterns of differential exclusions disclosed in our analysis, the question arises if similar

patterns might have affected the RCTs on flexible sigmoidoscopy. Four such trials have been conducted and reported [21−24], from which a CRC risk reduction by 21% has been estimated in a recent intention-to-screen pooled analysis [25]. In the trials from the UK [21], Italy [22], and the United States [23], preselection of people without previous CRC diagnosis was based on information from prerandomization contacts with all participants and/or the participants' general practitioners. Postrandomization exclusions due to previous CRC diagnosis were still reported, but their rates were much lower and not differential between the intervention and the usual-care groups. In the Norwegian flexible sigmoidoscopy trial, randomization was performed after selecting participants from population registries [24]. This procedure and the overall postrandomization exclusion proportions of participants with prior CRC diagnosis were similar as those in the NordICC trial, but the postrandomization exclusion proportions of participants with prior CRC were much more balanced between the invited group and the usual-care group. Hence, the specific pattern addressed in our manuscript seems to have been uniquely observed in the NordICC study, in which the vast majority of participants were recruited in Poland. This difference between the NordICC trial and the flexible sigmoidoscopy trials may partly explain the apparent and unexpected reported lack of stronger preventive effects of screening colonoscopy in preventing CRC compared to flexible sigmoidoscopy, despite the visualization of the entire colon and rectum.

The randomized design is undoubtedly a major asset of the NordICC trial, the first and so far only RCT on the long-term effects of the offer of screening colonoscopy on CRC risk and death, and successful completion of such a large multinational study over many years is an enormous achievement. It is the more crucial that the asset of the randomized design is not compromised by differential postrandomization exclusion proportions of CRC diagnoses in the comparison groups. Our analysis aimed to make a contribution to this end. In our study, we demonstrate that a seemingly modest, but nevertheless, statistically highly significant difference in postrandomization exclusions may have had far-reaching implications for the reported study results. We demonstrate that this difference, which so far received little if any attention in the discussion and interpretation of the NordICC trial results, may have led to the underestimation of screening effects. Our study may therefore help to more fully disclose the screening effects and encourage further investigation of this topic by the NordICC study group.

Nevertheless, our study also has limitations. The main limitation is that our analyses are exclusively based on published aggregate data, without the possibility to further explore the mechanisms behind the highly differential exclusion proportions in the study groups. Although the suggested reasons for the apparent discrepancy in postrandomization exclusions between the trial arms seem plausible, there may also be other reasons, which should be explored in further investigation. Our analyses suggest, however, that accounting for the differential exclusion proportions yields stronger screening effects, a finding which would hold regardless of the reasons underlying the differential exclusion proportions.

In conclusion, our reanalysis of published data of the first and so far only RCT on long-term effects of screening colonoscopy suggests stronger effects of screening colonoscopy after accounting for major differences in postrandomization CRC case exclusion proportions between the invited and the screened group. Further research should explore in more detail the mechanisms behind the differential postrandomization exclusion proportions of CRC cases and make every attempt to prevent or overcome potential bias resulting from such differential exclusions, both for CRC risk and related death. In addition, other major issues, such as the careful distinction between earlier detection of prevalent cases and prevention of truly incident cases by screening colonoscopy, or the completeness of 10-year follow-up, which have been addressed in detail elsewhere [16,26−29], deserve careful consideration in deriving clinical and public health implications of this most important and unique trial.

CRediT authorship contribution statement

Hermann Brenner: Writing − review & editing, Writing − original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Tim Holland-Letz:** Writing − review & editing, Methodology, Formal analysis. **Michael Hoffmeister:** Writing − review & editing. **Thomas Heisser:** Writing − review & editing.

Declaration of competing interest

There are no competing interests for any author.

Data availability

All analyses presented in this article are based on data that have previously been published elsewhere.

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