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LETTER TO THE JOURNAL

Unraveling the effects of screening colonoscopy on colorectal cancer early detection and prevention: the NordICC trial revisited

Based on intriguing findings from observational studies [1, 2], colonoscopy has since long been recommended for colorectal cancer (CRC) screening, long before evidence on its effectiveness in reducing CRC incidence and mortality was demonstrated by a randomized controlled trial (RCT). Such evidence has only recently been provided by the Nordic-European Initiative on Colorectal Cancer (NordICC) trial [3]. In this RCT, the risk of CRC was lower among those invited to undergo screening colonoscopy than among those not invited to screening. However, reported CRC risk reduction was smaller than anticipated: The authors derived risk ratios of 0.82 (95% confidence interval [CI] = 0.70-0.93) and 0.69 (95% CI = 0.55-0.83) in intention-to-screen analysis and adjusted per-protocol analysis, respectively, suggesting an 18% risk reduction of CRC among those invited for screening and a 31% risk reduction among screening attenders. These results have prompted major concerns and debate about the effectiveness and cost-effectiveness of screening colonoscopy [4], which had so far been considered as a particularly effective and cost-effective, if not cost-saving CRC preventive measure. However, the "incident" cases in the published NordICC trial results included CRCs that were already prevalent at recruitment and could not possibly have been prevented [5]. Such cases were early detected by screening among screening attenders, an additional desired screening effect. In the following, we demonstrate how to disentangle screening effects on CRC early detection and prevention.

Details on the design of the NordICC trial have been reported elsewhere [3]. Briefly, this trial was run in 4 Northern European countries (Poland, Norway, Sweden, and the Netherlands), but data from the Netherlands were not included for legal reasons in the first report on long-term effect estimates, published in October 2022. The study population for that analysis, which was drawn from population registries, included 84,585 presumptively healthy men and women 55-64 years of age who were randomized in a 1:2 ratio to either receive an invitation for a single colonoscopy or to usual-care. Recruitment was performed between 2009 and 2014. Of 28,220 participants in the invited group, 11,843 (42.0%) followed the invitation. Primary endpoints were risk of CRC incidence and death. Follow-up was performed by record linkage with cancer registries and cause-of-death registries.

During a median follow-up time of 10 years, 259 and 622 CRC cases were registered in the invited group and the usual-care group, respectively (Figure 1). Among the 259 CRC cases in the invited group, 102 were registered among attenders of screening colonoscopy, of which 62 were prevalent, screening-detected cases and 40 were truly incident cases. However, in the estimation of screening effects in the NordICC trial, no distinction was made between early detection of prevalent cases and prevention of incident cases. Rather, early detected prevalent cases and not prevented incident cases were conjoined in overall CRC risk estimates.

Our suggestion of an alternative analysis of the NordICC trial that unravels the effects of screening colonoscopy on CRC early detection and prevention is outlined in Figure 1. This analysis is based on just two very basic and plausible assumptions:

(i) Randomization in this very large trial ensured equal CRC risk in the intervention group and the usual care group ("standard RCT assumption").
(ii) Screening colonoscopy only prevented CRC among those who attended it, i.e., all prevented cases were prevented among screening attenders.

It is worth noting that this approach is unaffected by potentially different baseline risks in attenders or

List of abbreviations: CRC, colorectal cancer; RCT, randomized controlled trial; NordICC, Nordic-European Initiative on Colorectal Cancer; CI, confidence interval.

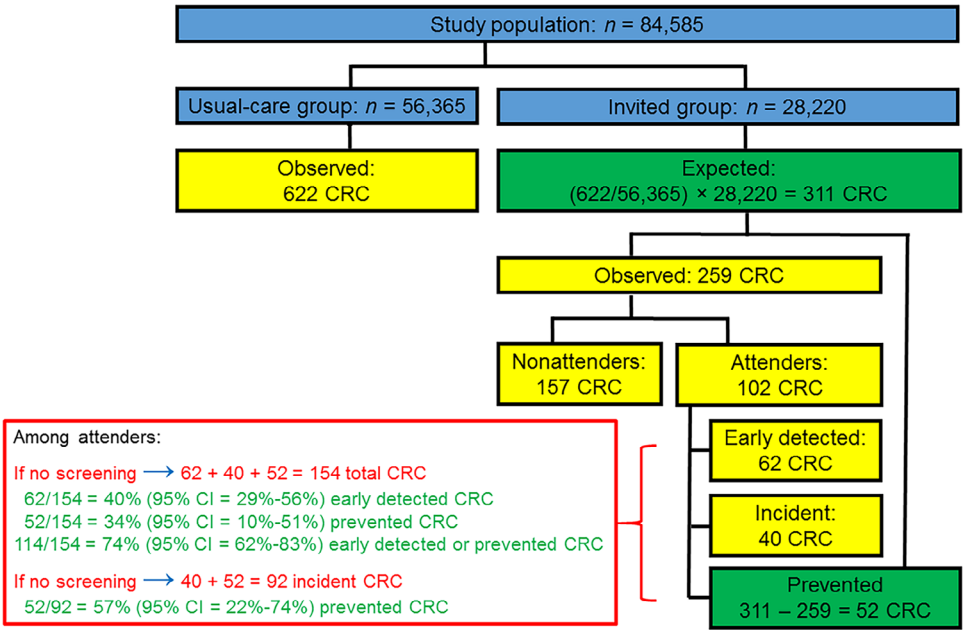

FIGURE 1 Alternative analysis of the NordICC trial results by which effects of screening colonoscopy on early detection of prevalent CRC cases and prevention of incident CRC cases are unraveled. The 95% CI for the estimated proportions were derived by Monte Carlo simulations as outlined in the Supplementary Materials and Methods.

non-attenders of screening, a common concern in standard per-protocol analyses.

Under these assumptions, the number of prevented cases among screening attenders can be estimated as the difference between the expected case number in the invited group in the absence of screening, which is given as 311 ([622/56,365] × 28,220) under the "standard RCT assumption" and the observed number ($n = 259$), i.e. as 52 (311 - 259). Hence, in the absence of screening, 154 (102 + 52) CRC cases would have been expected among the screening attenders, of which 62 (40%) were early detected at screening colonoscopy and 52 (34%) were prevented by detection and removal of CRC precursors at screening colonoscopy. Therefore, 114 (62 + 52) out of 154 CRC cases (74%) that were expected in the absence of screening were either early detected or prevented. Figure 1 also includes 95% CI for the estimated proportions which were obtained as the 2.5th and 97.5th percentile of one million runs of Monte Carlo simulations of the NordICC trial, using the observed case proportions as expected values.

In contrast to our analysis, the published analysis of the NordICC trial had implicitly included the 62 prevalent, early detected CRC cases among screening attenders as prevention failures in their risk estimtes. However, given that prevalent cases can be early detected but no longer be prevented, a more meaningful estimate of the proportion of prevented CRC is obtained as the proportion of the 52 prevented CRC among the 92 (52 + 40) potentially preventable incident CRC, i.e., as 57% (52/92).

Our analyses therefore disclose much stronger effects of screening colonoscopy than suggested by the original publication on that trial which reported an 18% risk reduction estimated by intention-to-screen analysis as its primary result and a 31% risk reduction among screening attenders estimated by adjusted per-protocol analysis (Supplementary Table S1). Although our analyses can be considered as a special type of per-protocol analyses in that they quantify effects among screening attenders, they are not prone to potential bias by differences in baseline risk of attenders and non-attenders of screening, which is a common concern for per-protocol analyses. Apart from the obvious fact that screening can only prevent CRC among those who use it, the only assumption needed for our analysis is the "standard RCT assumption", i.e. equal risk in the two randomized groups. In contrast to the original NordICC trial publication, our analysis considers early detection of prevalent, no longer preventable cases, which accounts for a substantial proportion of reduction of CRC mortality [6], as a desirable effect of screening colonoscopy rather than screening failure.

In the interpretation of the NordICC trial results one needs to be aware that the reported protective effects of colonoscopy were likely diluted by further factors, such as use of diagnostic colonoscopies outside the screening offer [7], and delayed registration of incident CRC cases [8]. Preventive effects of screening colonoscopy may therefore have been even substantially larger than those derived in our analysis.

In summary, we suggest an alternative analysis of the NordICC trial results which unravel effects of screening colonoscopy on CRC early detection and prevention. Our estimates are much more in line with previous results from observational studies demonstrating strong risk reduction among users of screening colonoscopy [1, 2] and real-world evidence on strong reduction of CRC incidence in populations with widespread screening colonoscopy use, such as the US [9]. We hope and trust that our analyses will help to resolve much of the major confusion caused by the original publication of the NordICC trial and encourage rather than discourage further efforts in CRC screening, for which screening colonoscopy is just one, albeit a particularly effective option [10]. Our analytical approach and results may also inform the design, planning and evaluation of screening strategies, not only for screening colonoscopy, but also other effective approaches of CRC screening, such as screening by flexible sigmoidoscopy or fecal immunochemical tests [10]. Finally, our approach may serve as a model for future analyses of RCTs on screening methods that lead to both early detection and prevention.

AUTHOR CONTRIBUTIONS

Hermann Brenner: conceptualization, methodology, statistical analysis, writing-original draft, and writing-review and editing. Tim Holland-Letz: methodology, statistical analysis, and writing-review and editing. Annette Kopp-Schneider: methodology and writing-review and editing. Thomas Heisser: conceptualization and writing-review and editing. Michael Hoffmeister: conceptualization and writing-review and editing. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This study was exclusively based on previously published aggregate data from the NordICC trial which had obtained ethical approval as reported in reference 3.

DATA AVAILABILITY STATEMENT

All data used for the calculations in this manuscript are included in Figure 1.

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SUPPORTING INFORMATION

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