NordICC Trial Results in Line With Expected Colorectal Cancer Mortality Reduction After Colonoscopy: A Modeling Study

Colonoscopy screening is a widely recommended method for detecting colorectal cancer (CRC) in countries across the world.[1] However, until recently, no randomized controlled trials demonstrated its effectiveness in average-risk individuals. Recently, Bretthauer et al[2] published preliminary results of a multicenter randomized controlled trial, the Nordic-European Initiative on Colorectal Cancer (NordICC) trial, that investigated the effects of once-only colonoscopy screening on CRC incidence and mortality.[2] In the intention-to-screen analysis, which compared participants not offered screening to those offered screening regardless of participation, they found that the invited group had an incidence and mortality reduction at 10 years of 18% and 10%, respectively. The investigators noted that although the incidence and mortality reductions were clinically important, they were lower than anticipated based on observational and modeling studies.

The publication of the NordICC trial results induced media attention and controversy regarding the effectiveness of colonoscopies.[3] Experts advised people to interpret the results cautiously, noting aspects of the NordICC trial that could contribute to the underwhelming findings. A critical issue was the low screening uptake (42%). In the adjusted per-protocol analyses, which compared participants not offered screening to those offered screening who received colonoscopy, incidence and mortality reductions at 10 years increased to 31% and 50%, respectively. Another important consideration was the relatively short 10-year follow-up period. This study aimed to evaluate whether the NordICC trial results are lower than expected based on modeling and to what extent the results could be explained by screening uptake and follow-up period.

We used 3 Cancer Intervention and Surveillance Modeling Network CRC models to simulate NordICC trial outcomes: Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRCSPIN), Microsimulation Screening Analysis Colorectal Cancer (MISCAN-Colon), and Simulation Model of Colorectal Cancer (SimCRC). Using these models, we simulated the NordICC trial population,[2] with 42% of the invited group simulated to receive a 1-time colonoscopy and a usual-care group remaining unscreened (Supplementary Table 1). Our modeling assumptions included random selection into screening unrelated to CRC risk, full adherence to US guidelines for adenoma surveillance,[4] and high sensitivity of colonoscopy (Supplementary Materials). We compared model predictions to reductions in CRC incidence and mortality observed in the trial. Additionally, we simulated 5 hypothetical scenarios: 42% adherence with 15- and 20-year follow-up and 100% adherence with 10-, 15-, and 20-year follow-up.

With 42% uptake and 10-year follow-up, the models predicted CRC incidence and mortality reductions of 11%–28% and 24%–32% (ranges are across models), respectively (Figure 1*A* and *B*). These estimates overlap the 95% confidence intervals (Cis) of the decreases observed in the NordICC intention-to-screen analyses, which were 18% (95% CI: 7–30) and 10% (95% CI: −16 to 36), respectively. The level of screening uptake had the largest impact on the findings: with 100% uptake, the model-predicted incidence and mortality reductions more than doubled to 26%–61% and 53%–70%, respectively (Figure 1*C* and *D*). These estimates compared well with reductions of 31% (95% CI: 17–45) and 50% (95% CI: 23–73), respectively, in the per-protocol NordICC analyses. Although the relative differences in risk reduction are substantial, the absolute incidence and mortality reduction only increased from 0.14%–0.29% to 0.31%–0.64% and from 0.10%–0.12% to 0.22%–0.26%, respectively, with 42% vs 100% uptake (Supplementary Figure 1).

With 42% uptake, the predicted incidence reduction increased to 18%–33% and 19%–35% at the 15- and 20-year follow-up, respectively (Figure 1*A*). With 100% uptake, these reductions increased to 40%–73% and 43%–77%, respectively (Figure 1*C*). Combining 100% uptake with a 15-year follow-up resulted in expected incidence and mortality reductions of 40%–73% and 59%–79%, respectively (Figure 1*C* and *D*).

In this study, we show that, in spite of suggestions otherwise,[2] model predictions are consistent with the NordICC trial results. As experts have pointed out, the results of the NordICC trial are largely determined by the screening uptake and the follow-up duration. Prior observational studies reported that colonoscopy was associated with a pooled CRC mortality reduction of 62% (range, 11%–88%) at an average follow-up of 8 years.[5] This is within the CI of the per-protocol NordICC trial results and in line with the modeling results, which estimated an average 63% CRC mortality reduction with 100% uptake and the 10-year follow-up.

A limitation of our study is that we assumed similar CRC risk for screening participants and nonparticipants. The trial results could be influenced by the healthy screenee effect, with people participating in screening at lower risk of CRC. If participants have a lower CRC risk than nonparticipants, this means that our models overestimate the effectiveness of screening. On the other hand, NordICC trial results show that the noninvited group had a higher risk of CRC than nonparticipants in the invited group,[2] suggesting that there was self-selection of higher-risk individuals participating in screening (eg, those with a family history of CRC or symptoms).

Abbreviations used in this paper: CRC, colorectal cancer; NordICC, Northern European Initiative on Colorectal Cancer.

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2023.06.035

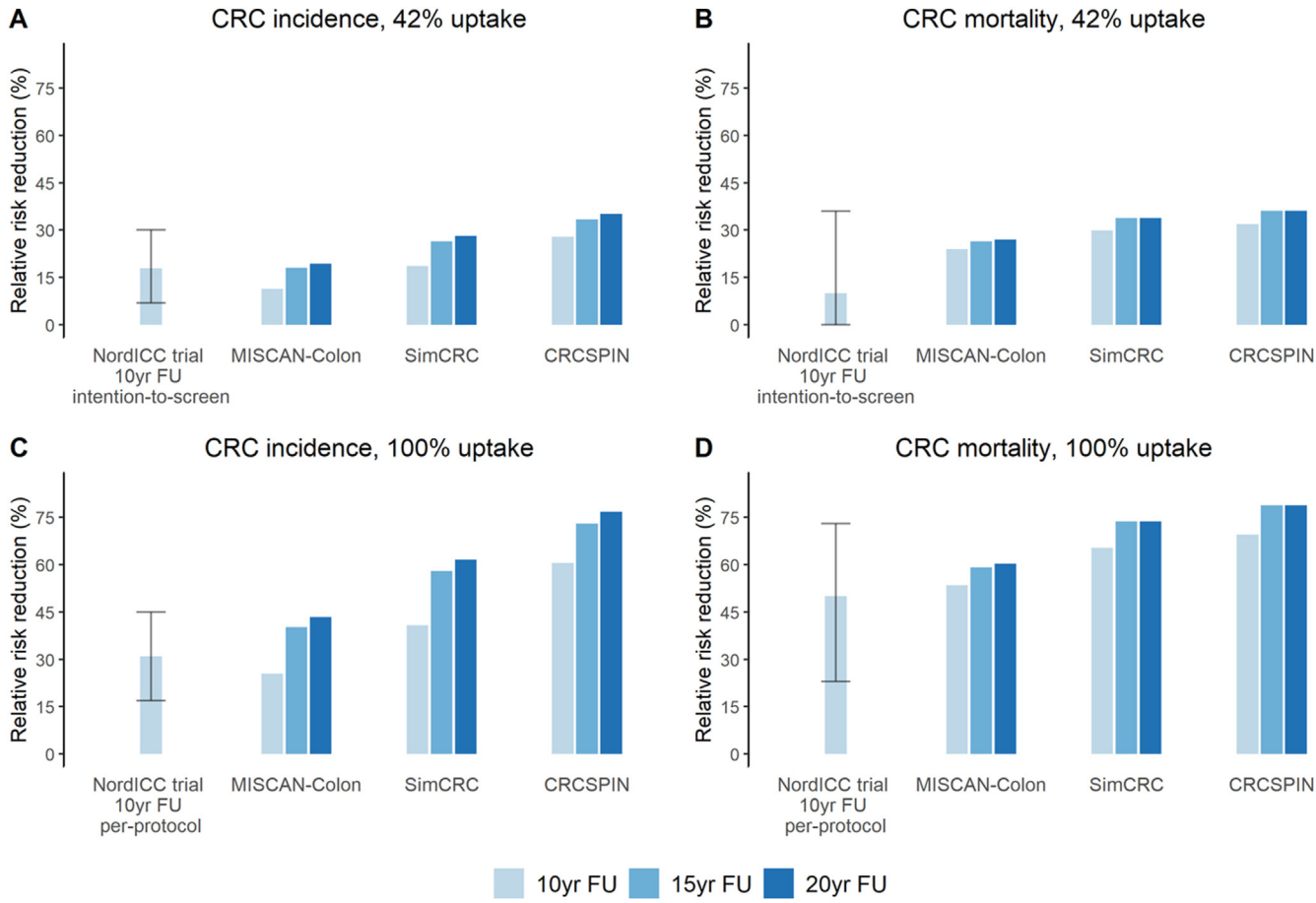


Figure 1. Relative risk reductions in CRC incidence (*A*, *C*) and CRC mortality (*B*, *D*) compared to no screening for 2 different uptake scenarios (42% and 100% uptake) and 3 different follow-up durations (10, 15, and 20 years). CRCSPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FU, follow-up; MISCAN-Colon, Microsimulation Screening Analysis Colorectal Cancer; SimCRC, Simulation model of Colorectal Cancer.

A higher CRC risk in participants than nonparticipants implies we may have underestimated screening effectiveness in our models. Systematic differences between screened and unscreened participants in the intervention group might explain differences between trial estimates of CRC mortality and model predictions. A second limitation concerns our assumed colonoscopy sensitivity. If the colonoscopy sensitivity achieved in the trial was lower than the sensitivity assumed when making model projections, then the projected benefits would be optimistic. Lower colonoscopy sensitivity would allow more adenomas to progress to cancer, reducing the effectiveness of colonoscopy.

The trial's 42% uptake aligns with the 5%–59% uptake reported in previous population-based studies.[6] Low participation, exemplified by the 42% uptake, may mute the population-level benefits of CRC screening, leading some to perceive it as disappointing. Nevertheless, it is crucial to emphasize that the individual-level benefit for participants, which is closer to the NordICC trial's adjusted per-protocol results, is more reassuring and reaffirms the effectiveness of the test. It is important to highlight that individuals who choose not to participate in screening do not receive any screening benefits, underlining the value of screening. Moreover, individuals should be aware that more favorable outcomes may be expected in the long term, especially beyond 15 years of follow-up, and that larger benefits could be achieved with repeated 10-yearly colonoscopy screening, as recommended in the United States. In conclusion, our findings show that NordICC trial results are consistent with anticipated mortality reductions from screening colonoscopy, and that with further follow-up higher benefits may be realized, especially in the NordICC's per-protocol analyses.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.06.035.

DANICA M.N. VAN DEN BERG
Department of Public Health
Erasmus MC University Medical Center
Rotterdam, The Netherlands

PEDRO NASCIMENTO DE LIMA
RAND Corporation
Arlington, Virginia

AMY B. KNUDSEN
Institute for Technology Assessment
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts

CAROLYN M. RUTTER
Biostatistics Program
Public Health Sciences Division
Fred Hutchinson Cancer Center
Hutchinson Institute for Cancer Outcomes Research
Seattle, Washington

DAVID WEINBERG
Department of Medicine
Fox Chase Cancer Center
Philadelphia, Pennsylvania

IRIS LANSDORP-VOGELAAR
Department of Public Health
Erasmus MC University Medical Center
Rotterdam, The Netherlands

THE CISNET-COLON GROUP

References

1. Schreuders EH, et al. Gut 2015;64:1637–1649.
2. Bretthauer M, et al. N Engl J Med 2022;387:1547–1556.
3. Krz S, et al. Nature 2023;613:235–237.
4. Gupta S, et al. Gastrointest Endosc 2020;91:463–485.e5.
5. Zhang J, et al. J Cancer 2020;11:5953.
6. Holden DJ, et al. Ann Intern Med 2010;152:668–676.

Received March 7, 2023. Accepted June 28, 2023.

Correspondence
Address correspondence to: Danica M. N. van den Berg, MSc, Erasmus MC, Room NA-23, PO Box 2040, 3000 CA Rotterdam, The Netherlands. e-mail: d.m.n.vandenberg@erasmusmc.nl.

Acknowledgments
The CISNET-Colon Group includes Ann G. Zauber,[1] Anne I. Hahn,[1] Fernando Alarid Escudero,[2] Christopher E. Maerzluft,[3] Alexandra Katsara,[4] Karen M. Kuntz,[5] John M.Inadomi,[6] Nicholson Collier,[7] Jonathan Ozik,[7] Luuk A. van Duuren,[4] Rosita van den Puttelaar,[4] Matthias Harlass,[4] Claudia Leigh Seguin,[8] Barak Davidi,[8] Carlos Pineda-Antunez,[9] Eric J. Feuer,[10] and Lucie de Jonge[4]; from the [1]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; [2]Department of Health Policy, School of Medicine, and Stanford Health Policy, Freeman-Spogli Institute for International Studies, Stanford University, Stanford, California; [3]Fred Hutchinson Cancer Center, Hutchinson Institute for Cancer Outcomes Research, Biostatistics Program, Public Health Sciences Division, Seattle, Washington; [4]Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [5]Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, Minnesota; [6]Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [7]Decision and Infrastructure Sciences, Argonne National Laboratory, Lemont, Illinois; [8]Institute for Technology Assessment, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts; [9]Global Health Cost Consortium (CISIDAT), Morelos, Mexico; and [10]Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland.

CRediT Authorship Contributions
Danica van den Berg, MSc (Conceptualization: Equal; Formal analysis: Lead; Writing – original draft: Lead).
Pedro Nascimento de Lima, PhD (Conceptualization: Equal; Formal analysis: Supporting; Writing – review & editing: Equal).
Amy B. Knudsen, PhD (Conceptualization: Equal; Formal analysis: Supporting; Writing – review & editing: Equal).
Carolyn M. Rutter, PhD (Conceptualization: Equal; Writing – review & editing: Equal).
David Weinberg, MD, MSc (Conceptualization: Equal; Writing – review & editing: Equal).
Iris Lansdorp-Vogelaar, PhD (Conceptualization: Equal; Supervision: Lead; Writing – review & editing: Equal).

Conflicts of interest
The authors disclose no conflicts.

Funding
This research was supported by grant U01-CA253913 from the National Cancer Institute as part of the Cancer Intervention and Surveillance Modelling Network (CISNET). Ann G. Zauber is also supported by P30 CA008748 at Memorial Sloan Kettering Cancer Center. This research used resources of the Argonne Leadership Computing Facility, which is a Department of Energy Office of Science User Facility supported under contract DE-AC0206CH11357. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability
Model results and R code for figures are available upon request.

Supplementary Materials

Model Descriptions

This study used 3 independently developed microsimulation models: Microsimulation Screening Analysis for Colorectal Cancer (MISCAN-Colon), Simulation Model of Colorectal Cancer (SimCRC), and Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRCSPIN). Each model has a natural history and a screening component, summarized below.

Natural History Component

All models describe the natural history of CRC in an average-risk unscreened population. We assumed that all CRC develops through the adenoma-carcinoma pathway and that simulated persons are free of diagnosed CRC until screening in 2012. Each simulated individual can develop 1 or more colorectal lesions. Lesions may proceed through 3 phases: a noninvasive adenoma phase, a preclinical cancer phase, and a clinical cancer phase. Persons may die of other causes at any time.

Each model's natural history component was initially calibrated to Surveillance, Epidemiology, and End Results (SEER) data for the period 1975–1979. To adjust the models for CRC risk differences between SEER 1975–1979 and Norway and Poland, we compared CRC incidences in the countries. The magnitude of the difference was estimated by the ratio of CRC incidence in Norway and Poland between 2009 and 2010 relative to SEER data from 1975–1979 (Supplementary Table 1). We assumed that the decreased risk arises from changes in adenoma onset, not from slower progression of adenomas to CRC.

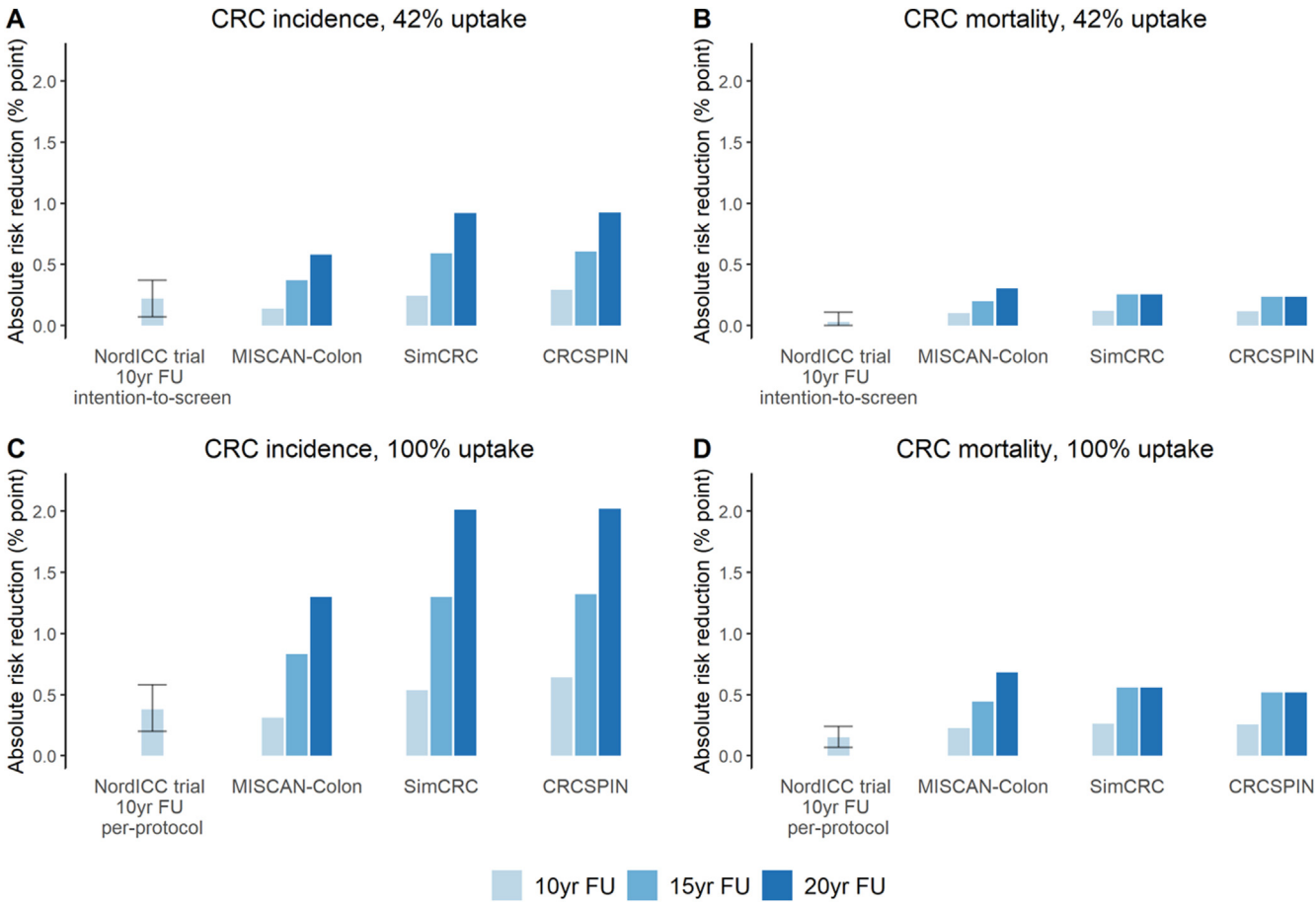
Screening Component

Screening will alter some of the simulated life histories: some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable survival. The ability of a test to detect lesions depends on its sensitivity. These sensitivities are lesion based. We assumed a colonoscopy sensitivity of 0.75, 0.85, 0.95, and 0.95 for adenomas of 1 to $<$6 mm, adenomas of 6 to $<$10 mm, adenomas of $\geq$10 mm, and CRC, respectively. We assumed the same sensitivities for surveillance colonoscopy as for screening colonoscopy.

Moreover, we assumed that individuals with an adenoma detected undergo colonoscopy surveillance according to the Multi-Society Task Force guidelines.[5] We assumed persons with adenoma findings are perfectly adherent with the surveillance colonoscopy schedules. Additionally, we assumed that persons in whom adenoma(s) have been detected remain on surveillance until age 85 years, provided that no adenomas are detected at the last surveillance colonoscopy. If adenomas are detected, then surveillance continues according to the clinical findings at the last colonoscopy until the person has a colonoscopy with no adenomas detected.

Outcomes

Outcomes were simulated for 10 different birth cohorts (birth years ranging from 1948 to 1957). For each cohort, we simulated 2 strategies: (1) no screening and (2) once-only colonoscopy in 2012 with 100% adherence and surveillance for people with adenomas detected. The results of the different strategies were consolidated afterward in the postprocessing based on the screening participation of the trial participants.[3] All outcomes were tallied by year from 2012 onward. The primary outcomes included the number of CRC cases and CRC deaths.



Supplementary Figure 1. Absolute risk reductions in CRC incidence (*A*, *C*) and CRC mortality (*B*, *D*) compared to no screening for 2 different uptake scenarios (42% and 100% uptake) and 3 different follow-up durations (10, 15, and 20 years). CRCSPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FU, follow-up, MISCAN-Colon, Microsimulation Screening Analysis Colorectal Cancer; SimCRC, Simulation Model of Colorectal Cancer.

Supplementary Table 1. CRC Age-Adjusted (World Population) Incidence Rates for SEER 1975–1979, Norway 2009–2010, and Poland 2009–2010 and CRC Incidence Rate Ratios Among Norway and Poland 2009–2010 vs SEER 1975–1979

Period	CRC cases per 100,000	CRC rate ratio
SEER, 1975–1979	39.3	1
Norway, 2009–2010	39.8	1.0
Poland, 2009–2010	25.3	0.6

NOTE. Source for Poland and Norway data: European Cancer Information System (https://ecis.jrc.ec.europa.eu).