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Colonoscopy Screening and Colorectal Cancer Incidence and Mortality

January 26, 2023
N Engl J Med 2023; 388:376-379
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Metrics

TO THE EDITOR

In the Nordic-European Initiative on Colorectal Cancer (NordICC) trial, conducted by Bretthauer et al. (Oct. 27 issue),[1] two separate questions were asked. First, in a population in which screening colonoscopy was uncommon, what percentage of persons 55 to 64 years of age who had not undergone the procedure previously would accept an invitation to undergo one? Second, among those who would, how much would the incidence of and mortality from colon cancer be reduced?

Most reports by the media about this trial did not show the answer to the first question, namely 42% (itself an average of three country-specific values: 33%, 61%, and 40%). Instead the reports focused on the intention-to-treat analyses that the abstract was limited to (reductions of 18% and 10% in colorectal cancer incidence and mortality, respectively) and used headlines that questioned the benefits of colonoscopy.

This pooling of results from the 42% who might and the 58% who could not benefit from screening colonoscopy conflates the first and second questions and yields numbers that do not speak to individual patients or their physicians. Only a few journalists reported the message of the full text, which answers both the first question (i.e., 42%) and the second question (i.e., 31% and 50%). The abstract, which contained only the intention-to-treat analyses, led most journalists to miss the first question and answer the second question incorrectly.

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No potential conflict of interest relevant to this letter was reported.

1 Reference

TO THE EDITOR

Colonoscopy achieves its aim only if it interrupts the long natural history going from adenoma to carcinoma, growth, symptoms (often bleeding), treatment, metastasis, and death. Even the first of these steps, malignant transformation, is thought to take 10 to 15 years,[1] and at 10 years of follow-up, more than two thirds of the cases in the control group that could have had their course altered by screening detection would not even be diagnosed yet, let alone have proved fatal.[1]

Bretthauer et al. found a high number of participants with screen-detected adenomas (3634 participants) and a substantial reduction in the incidence of cancer (57 cases avoided — an 18% reduction) but few deaths averted (8 — a 10% reduction), findings that have led some commentators to call for a reassessment of the usefulness of colonoscopy.

Without colonoscopy, how many of the equivalent adenomas will progress and prove fatal in the control group? Further follow-up will answer this question, but after 10 years of follow-up, it is still far too soon to say. This trial and the responses to it show the need to reassess and understand not the usefulness of colonoscopy but rather the timing of its benefits.

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No potential conflict of interest relevant to this letter was reported.

1 Reference

TO THE EDITOR

In the interim report by Bretthauer et al., a per-protocol analysis showed a 31% reduction in the incidence of colorectal cancer and a 50% reduction in mortality from colorectal cancer, findings that confirm earlier observations[1,2] and provide further evidence for the adenoma–carcinoma concept and for the prevention of colorectal cancer and related deaths by means of colonoscopic polypectomy. However, high adherence to screening is critical for its effectiveness. The "real life" effectiveness in the NordICC trial was disappointing — only 42% of the participants adhered to colonoscopy.

Are these intention-to-treat observations applicable to other clinical environments? In the United States, screening campaigns including colonoscopy directed to the public and to health care professionals were mounted over decades with congressional legislation and involvement of the media.[3] These campaigns may have enhanced adherence to colonoscopy in many U.S. programs. The design of the NordICC trial did not allow for the enrollment of participants from regions where screening programs had been initiated. It would be interesting to learn about the colonoscopy information environment and campaigns in the countries participating in the NordICC trial and in the ongoing screening colonoscopy trials. Although we look forward to the planned 15-year follow-up of the NordICC trial, the data thus far support present guidelines including colonoscopy, especially in the U.S. population.[4]

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No potential conflict of interest relevant to this letter was reported.

4 References

TO THE EDITOR

In the international NordICC randomized trial, Bretthauer et al. compared the effectiveness of a once-only invitation for screening colonoscopy with no invitation. The authors commented that offers for colonoscopy in the control group from sources outside the trial (screening contamination) were minimal.

An even more important reason for the lower-than-expected effectiveness of screening colonoscopy in the trial that was not addressed by the authors is that the use of diagnostic colonoscopies during the follow-up period was common.[1] The protection provided with diagnostic colonoscopies through the detection and removal of precursors of colorectal cancer is similar to that with screening colonoscopy. It is highly likely that during follow-up, such colonoscopies were more often performed in the participants in the usual-care group, who had no offer of screening colonoscopy at baseline, than in those in the invited group, thereby leading eventually to a lower colorectal cancer incidence and mortality in the usual-care group.[2,3] The estimated effectiveness of screening colonoscopy in this trial could thus be diluted, lower than expected, and lower than what existing evidence of the effects of screening colonoscopy would suggest.[4]

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No potential conflict of interest relevant to this letter was reported.

4 References

TO THE EDITOR

We address the criticism in the editorial by Dominitz and Robertson[1] accompanying the NordICC trial that the unexpectedly low colonoscopic detection rate of adenoma of 31% in the trial may have prevented a benefit of colonoscopy in significantly reducing overall mortality. The low adenoma detection rate in western European countries as compared with the higher rate in the United States may be due in part to known higher risk factors for adenomas in the U.S. population, including a much higher prevalence of obesity (30% vs. 12%), a higher rate of ever having smoked cigarettes, higher fat and cholesterol consumption, and poorer physical fitness.[2,3] We think that the adenoma detection rate reported in the NordICC trial may be appropriately lower in European populations than in U.S. populations and that this rate should not necessarily be viewed as a shortcoming of the trial.

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No potential conflict of interest relevant to this letter was reported.

The opinions expressed in this letter are those of the authors alone and are not necessarily those held by their employers at the Veterans Affairs hospitals or the U.S. government.

3 References

RESPONSE

The authors reply: The NordICC trial was not designed to assess population participation in colonoscopy screening, as Hanley implies. We investigated population-level effectiveness of colonoscopy screening and assumed 50% participation, as explained in the trial protocol. The effectiveness of a population screening program is best measured by the intention-to-treat effect on colorectal cancer incidence and mortality, as highlighted in the abstract. We agree with Hanley that per-protocol analyses, although prone to bias and not as trustworthy as intention-to-treat analyses, are important for individual decision making. We have therefore provided these analyses, both in the main text of our article and in the Supplementary Appendix, available with the full text of the article at NEJM.org.

In response to Deck: we think that before the publication of our article, most investigators would have agreed that 10 years is a reasonable period to assess the benefits of colonoscopy screening. This is how the results of previous sigmoidoscopy trials were reported[4] and how two other ongoing colonoscopy screening trials are designed.[5] A 10-year colonoscopy screening interval is also widely endorsed by professional societies. Fortunately, our trial is ongoing, and whether 10 years is too short to assess the benefits of colonoscopy screening will be helpful to see in future analyses.

We do not agree with Winawer and Hanley that the achieved 42% participation in our trial is low — it is close to the 50% participation that we expected when we designed the trial and is higher than that in many colonoscopy screening studies.[1,2] In the United States, where colonoscopy screening has been promoted for many years, participation is approximately 60%, which is similar to the participation in Norway in our trial.[3] The screening benefits with respect to the incidence of colorectal cancer in Norway are provided in Table S5 in the Supplementary Appendix of our report. These results may serve to inform the current population-level effectiveness of colonoscopy screening in the United States.

The results of our per-protocol analyses indicate that colonoscopy screening may reduce mortality from colorectal cancer by as much as 50% and are thus in line with what some observational studies have estimated, as Winawer points out. We would caution against overinterpretation at this time of follow-up because the number of deaths to date was small, and thus estimates are uncertain. Forthcoming analyses with longer follow-up will shed more light on this important topic.

Hoffmeister et al. are concerned about the dilution of screening benefits by more colonoscopies for clinical indications in the control (no-screening) group. We have been able to track colonoscopy activities in Norway through the national quality network Gastronet and in Poland through the National Health Fund registry and did not observe more diagnostic colonoscopies in the control group than in the intervention group.

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Since publication of their article, the authors report no further potential conflict of interest.

5 References

RESPONSE

The editorialists reply: In response to Cappell et al.: our editorial aimed to place the recently published NordICC trial into perspective. We did suggest that the quality of colonoscopy in that trial may have contributed to a lower-than-expected benefit from colonoscopy in the intention-to-treat analysis, since 29% of endoscopists who performed at least 30 colonoscopies had an adenoma detection rate below the 25% minimum benchmark recommended in both the United States and Europe.[1,2] We agree that the incidence of colorectal cancer varies among countries, and by extension, the adenoma detection rate would be expected to vary as well. However, the age-standardized incidences of colorectal cancer per 100,000 adults 55 to 64 years of age (the age range in the NordICC trial) are substantially higher in Norway and Poland than in the United States (130.6 and 112.1, respectively, vs. 90.3), and the incidence is equal in the United States and Sweden (90.3).[3] So, to the extent that the development of colorectal cancer is similar in these countries (i.e., through an adenoma–cancer sequence), we would not expect the adenoma detection rate in those countries to be markedly lower than that in the United States.

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Since publication of their editorial, the authors report no further potential conflict of interest.

3 References

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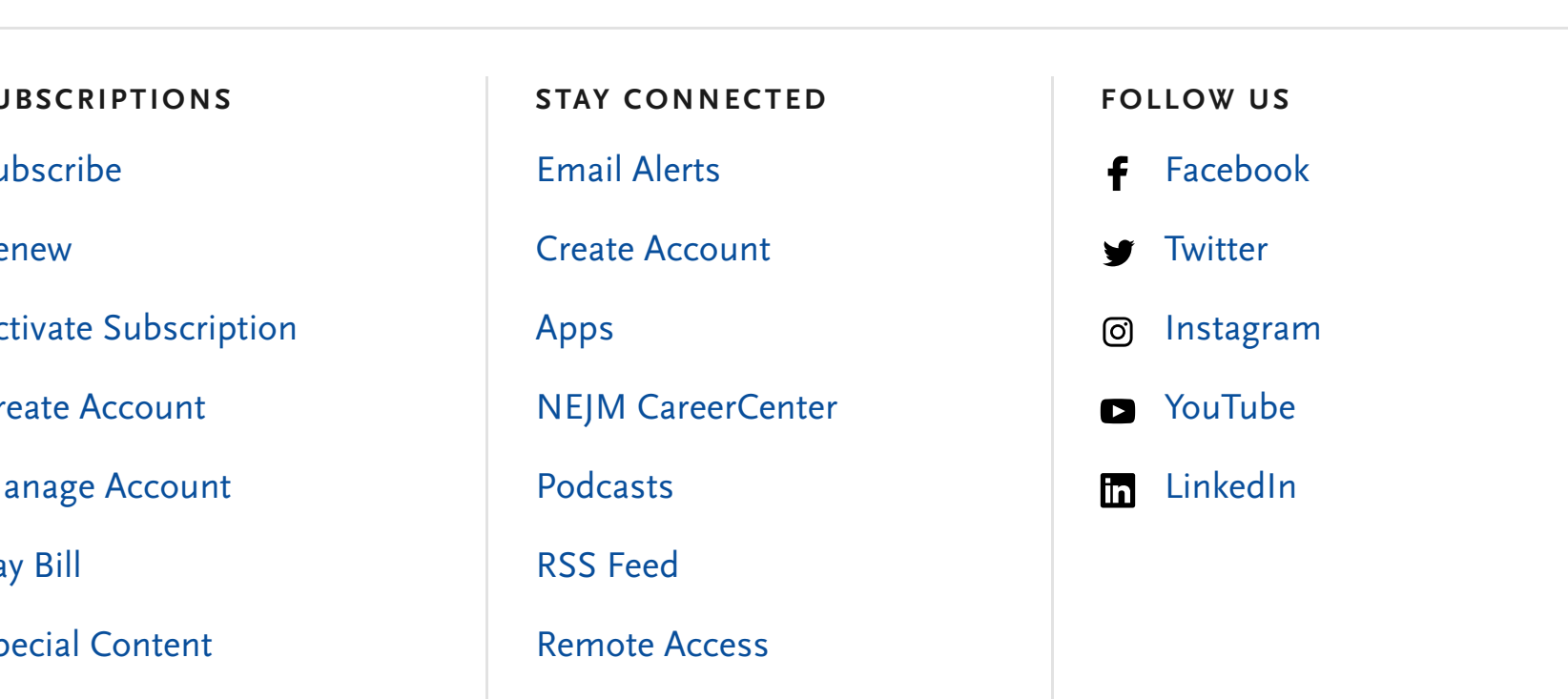

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