EDITORIAL

Understanding the Results of a Randomized Trial of Screening Colonoscopy

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For more than two decades, colonoscopy has been recommended as one of several available options for colorectal cancer screening, and it has been the predominant form of screening for colorectal cancer used in the United States. However, the best evidence to support its use has been limited to data from cohort studies, which have estimated that this type of screening has been associated with a 40 to 69% decrease in the incidence of colorectal cancer and a 29 to 88% decrease in the risk of death from this disease.[1] Unlike randomized, controlled trials, which have provided support for fecal occult blood testing and sigmoidoscopy,[2] cohort studies probably overestimate the real-world effectiveness of colonoscopy because of the inability to adjust for important factors such as incomplete adherence to testing and the tendency of healthier persons to seek preventive care.

This evidence gap is addressed by the landmark Nordic-European Initiative on Colorectal Cancer (NordICC) trial, the results of which are now reported in the *Journal* by Bretthauer et al.[3] This pragmatic trial involved nearly 85,000 men and women who were randomly assigned either to receive an invitation to undergo screening colonoscopy or to receive usual care (i.e., no screening). In the intention-to-screen analysis, colonoscopy was found to reduce the risk of colorectal cancer over a period of 10 years by 18% (risk ratio, 0.82; 95% confidence interval [CI], 0.70 to 0.93). However, the reduction in the risk of death from colorectal cancer was not significant (risk ratio, 0.90; 95% CI, 0.64 to 1.16).

This relatively small reduction in the risk of colorectal cancer and the nonsignificant reduction in the risk of death are both surprising and disappointing; these findings raise the question of why previous studies would have shown greater effectiveness of sigmoidoscopy than colonoscopy. In fact, a pooled analysis of four large, randomized sigmoidoscopy trials showed significant reductions in both the incidence of colorectal cancer and the risk of related deaths (22% and 26%, respectively).[2]

There are several potential explanations for these discouraging results. For example, screening can be effective only if it is performed; only 42% of the participants in the NordICC trial who were invited to undergo screening underwent colonoscopy, as compared with 58 to 87% in the sigmoidoscopy trials.[4] In the adjusted per-protocol analysis of the NordICC trial, colonoscopy was estimated to reduce the incidence of colorectal cancer by 31% and the risk of colorectal cancer–related death by 50%, findings that approximated those of cohort studies. Although consent after randomization, as used in this trial, offers some advantages over consent before randomization with respect to estimating adherence to population-based screening efforts, participation in countries where screening colonoscopy is not well established may be very different than that in countries (e.g., the United States) where its use is broadly recommended. Therefore, the actual effectiveness of colonoscopy in populations that are more accepting of colonoscopy could more closely resemble the effectiveness shown in the per-protocol analysis in this trial.

Another explanation for these results is that the benefits of screening colonoscopy take time to be realized, because the incidence of colorec-

tal cancer is initially increased when presymptomatic cancers are identified. With the use of polypectomy, the future risks of colorectal cancer and related death can be reduced[5] if polyp resection is adequate.[6] The NordICC investigators plan to repeat their analysis at 15 years.

Another consideration with respect to the results of the trial is that colonoscopy is highly operator dependent. The proportion of screening colonoscopies in which one or more adenomas is detected is called the adenoma detection rate. Endoscopists with a higher adenoma detection rate offer their patients greater protection from the risks of colorectal cancer and related death than endoscopists who find fewer precancerous polyps. One study showed that every 1 percentage-point increase in the adenoma detection rate is associated with a 3% reduction in the future incidence of colorectal cancer and a 5% reduction in colorectal cancer–related death.[7] Bretthauer et al.[8] previously reported that in the NordICC trial, 29% of the endoscopists had an adenoma detection rate below the recommended minimum threshold of 25%.[9]

Finally, some data from the trial suggest that high-risk persons in Poland tended to choose to undergo colonoscopy; rates of detection of colorectal cancer were high, and the incidence of colorectal cancer was lower among participants in the invited group who did not undergo screening than among those in the usual-care group. Therefore, it is plausible that some persons agreed to participate in the trial and undergo screening because of an underlying concern about symptoms. If true, this would lead to an underestimation of the per-protocol effectiveness of colonoscopy and would also help to explain why the expected shift toward detection of earlier-stage colorectal cancer with screening colonoscopy was not observed.

The results of this trial are unique and important. Another large, randomized trial is the ongoing SCREESCO (Screening of Swedish Colons) trial comparing colonoscopy with either a fecal immunochemical test (FIT) performed every 2 years or usual care (no screening).[10] However, a preliminary report of the SCREESCO trial showed that only 35% of the participants who were invited to undergo colonoscopy underwent the procedure, and the endoscopists had a median adenoma detection rate of 20%. Two other large trials comparing colonoscopy with either FIT every 2 years[11] or annual FIT[12] may eventually shed additional light on the relative effectiveness of colonoscopy, although these trials do not include a comparison of colonoscopy screening with no screening.

Given the modest effectiveness of screening colonoscopy in the NordICC trial, what should we conclude about the role of this test? If the trial truly represents the real-world performance of population-based screening colonoscopy, it might be hard to justify the risk and expense of this form of screening when simpler, less-invasive strategies (e.g., sigmoidoscopy and FIT) are available. However, with increased levels of participation in screening and with high-quality examinations, greater reductions in the incidence of colorectal cancer and related death would be expected. Although the results reported by Bretthauer et al. may, in the near term, temper enthusiasm for screening colonoscopy, additional analyses, including longer follow-up and results from other ongoing comparative-effectiveness trials, will help us to fully understand the benefits of this test.

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