Sigmoidoscopy Screening Probably Works, but How Well Is Still Unknown

Jack S. Mandel

The most persuasive scientific evidence for the benefit of a cancer screening test comes from a randomized controlled clinical trial (RCT) where the endpoint is a reduction in mortality from (or incidence of) the disease of interest. There have been three RCTs of a fecal occult blood test (Hemoccult; Beckman Coulter, Palo Alto, CA) for early detection of colorectal cancer involving more than 250 000 people that have shown consistent results (1–5). Unfortunately, for the other colorectal cancer screening methods (i.e., sigmoidoscopy, colonoscopy, virtual colonoscopy, barium enema, and other fecal occult blood tests), there is no adequately completed trial that provides a valid estimate of the effect of screening. RCTs are currently underway to evaluate sigmoidoscopy (6,7), and a pilot study has been implemented to examine the benefits associated with a one-time colonoscopy (8). Of the tests that have not undergone adequate

Correspondence to: Jack S. Mandel, Ph.D., M.P.H., Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd. NE, Atlanta, GA 30322 (e-mail: jsmande@sph.emory.edu).

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evaluation but are still generally recommended (i.e., sigmoidoscopy, colonoscopy, and double-contrast barium enema), it is likely that all are effective. However, the extent to which they reduce mortality (or incidence) is not known. Thus, it is difficult to accurately assess the cost-effectiveness of those tests or to determine the appropriate screening interval.

With almost one million new cases of colorectal cancer diagnosed worldwide each year (9), we are fortunate to have so many screening tests to detect this disease at an early (and potentially) treatable stage. The challenge is to decide how to increase screening compliance and how to use the tests in the most cost-effective manner. Herein lies the problem, because the effectiveness of all the screening methods except the Hemoccult test is not known and the results from observational (largely case–control) studies may not provide a valid estimate of the screening effect because of potential selection, information, lead-time, and length biases [for example, see (10–19)].

In an RCT of screening, eligible individuals are randomly assigned to a screened or a usual care (control) group, thus increasing the likelihood of comparability between the groups. A fundamental problem with case–control studies of screening is selection bias, which occurs because those who are screened have self-selected, that is, they have elected to be screened, and those who have not been screened have refused the offer of screening or for some other reason have not been offered screening. If the mortality rate from the disease of interest in the absence of screening is different between those who accept screening and those who refuse screening, then a bias of unknown magnitude and direction occurs. This bias in the estimate of the screening effect would also apply to a study where incidence is the endpoint. The other biases mentioned above can also affect the results of case–control studies.

Although it is difficult to determine the direction and magnitude of the bias, in general, case–control studies may overestimate the effectiveness of the screening test relative to the RCT. In an RCT, the effect of screening is usually underestimated because some individuals assigned to the screened group do not comply and some individuals assigned to the control group obtain the screening test through other means. Demissie et al. (20) compared results from RCTs for breast cancer screening with results from case–control studies of breast cancer screening and found that the case–control studies provided statistically significantly lower risk estimates (i.e., they demonstrated a more favorable screening effect) than the RCTs. The potential for selection bias (or confounding) is further illustrated in the study by Slattery et al. (21), in which people who reported having a screening sigmoidoscopy were more likely to consume a diet higher in fiber, fat, and calcium and lower in red meat and fat than people who reported having no screening sigmoidoscopy. Kavanaugh et al. (22) found similar associations. These issues can be addressed provided the investigators collect data on lifestyle factors that could confound the relationship between screening and the disease and consider those factors in the analysis.

There have been a number of case–control studies of sigmoidoscopy screening and all have suggested a benefit [for example, see (21–29)]. Although the U.S. Preventive Services Task Force determined that the evidence from case–control studies of sigmoidoscopy was sufficient to include this test in their screening recommendations, they did not specify a screening interval (30). In this issue of the Journal, Newcomb et al. (31) attempt to address the issue of screening interval in a population-based case–control study of individuals aged 20–74 years. Case patients newly diagnosed with invasive colorectal adenocarcinoma between 1998 and 2002 were ascertained from the SEER registry, and control subjects, frequency-matched to the case patients on age and sex, were selected from state driver’s license data (for those aged 20–64 years) or from the Centers for Medicare and Medicaid Services (Baltimore, MD) files (for those older than 64 years). It is unclear whether the control subjects were identified during the same years as the case patients. Failure to do so could have introduced a bias, because eligible control subjects who left the study area before selection would not have had the opportunity to participate in the study.

In the Newcomb et al. study, the case patients and control subjects were interviewed by telephone to obtain their screening histories and other demographic and personal information. Twenty-three percent of the eligible case patients and 32% of the eligible control subjects did not participate at all or did not provide complete information. There was no validation of the self-reported information, particularly the information on screening sigmoidoscopy. This lack of validation is important because some of the analyses were based on small numbers, and misclassification of only a few cases could substantially affect the risk estimate. As shown in Table 1 of the article by Newcomb et al., the number of case patients who reported having a sigmoidoscopy ranged from three to nine for the different time intervals that were analyzed. Although a number of covariates were included in the analyses, important lifestyle factors, such as physical activity and diet, were not.

The results suggested that the incidence of distal cancers was reduced by 70% among those reporting a single screening sigmoidoscopy and by 76% among those who ever had a sigmoidoscopy (including those who had multiple screening tests). This effect was observed for up to 7 years for the single test and for up to 10 years for any test. The observed incidence reduction in the distal colon would translate to an overall incidence reduction of 35%–42% from a single test, assuming that 50%–60% of cancers are detectable by sigmoidoscopy. Adjusting for noncompliance and possible biases (if this was possible) might further reduce this estimate. A further consideration is the age group that Newcomb et al. studied. Case patients were 20–74 years old. Current screening recommendations apply to people 50 years old or older. Extrapolating the findings from the Newcomb et al. study to a population that was 50 years old or older would further reduce the overall screening effect because the percentage of lesions beyond the reach of the flexible sigmoidoscope appears to increase with age (32,33), thus a greater percentage would be missed in the older population.

Newcomb et al. demonstrate that a single sigmoidoscopy is associated with a large reduction in the incidence of colorectal cancer and suggest that the current recommended screening interval of 5 years could be lengthened. It would be premature to do so on the basis of results from this case–control study. A more precise estimate of the benefit from sigmoidoscopy screening will have to await the results from the ongoing RCTs. At that time, we will be in a better position to more accurately evaluate the risks, benefits, and cost-effectiveness of screening. Those results will provide a better basis on which to develop screening policy.
REFERENCES


Note

1 Editor’s note: SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.