Screening Flexible Sigmoidoscopy Reduces Colon Cancer Incidence and Mortality, But Compared with What?

Schoen RE, Pinsky PF, Weissfeld JL, et al; PLCO Project Team. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345–57.

Study Overview

Objective. To determine whether screening flexible sigmoidoscopy reduces colorectal cancer (CRC) incidence and mortality.

Design. Randomized trial.

Setting and participants. 154,900 men and women aged 55 to 74 years were enrolled between 1993 and 2001 at multiple U.S. medical centers and block randomized to either endoscopic CRC screening with flexible sigmoidoscopy (n = 77,445) or usual care (n = 77,455). Patients were excluded from the study if they had a history of prostate, lung, ovarian, or colorectal cancer or were undergoing current treatment for any other cancer (except for basal or squamous cell cancers of the skin). Patients were also excluded if they had already undergone lower endoscopy in the 3 years prior to enrollment.

Intervention. Patients in the treatment arm underwent flexible sigmoidoscopy at baseline and again at 3 or 5 years (patients enrolled prior to 1995 were on the 3-year follow-up schedule). Screening procedures were performed by physicians and nurses associated with the study and based on a standardized protocol. Patients who had polyps or masses detected on screening were considered to have had a "positive" test result; however, any necessary follow-up and diagnostic procedures (including biopsy of a polyp or mass) were referred to the primary care team for management. Patients randomized to usual care did not receive sigmoidoscopies via the research team, but otherwise could receive any form of screening for colon cancer at the discretion of their primary care physician. A more detailed description of the usual care arm is not available as part of this publication. After randomization and initial screening, patients were followed from afar using mailed annual questionnaires and medical record review to determine their outcomes.

Main outcome measure. The main outcome measure was death from colorectal cancer, which was determined through mailed annual follow-up surveys and telephone calls then corroborated using the National Death Index. Attribution of death to colorectal cancer specifically, as opposed to another cancer in patients with multiple

diagnoses, was performed in a blinded fashion. The investigators also used surveys to collect information on colorectal cancer incidence and stage at diagnosis, overall survival/mortality, and complications of screening, and verified this information with targeted medical record review. Patients were considered to have colorectal cancer detected by the screening test if a diagnosis was made within 1 year after a positive endoscopy. The investigators classified colorectal cancers by location, either as "distal" (occurring in the rectum through splenic flexure), or "proximal" (occurring in the transverse colon through cecum).

Because all care was referred to the primary clinical team after the initial encounter, many patients in both arms received endoscopies (both colonoscopy and sigmoidoscopy) that were unassociated with the clinical trial. The investigators performed an additional questionnaire on just under 10% of participants at 5 years post-enrollment to determine what percent of patients in each arm had likely been "contaminated" by these off-study procedures. The survey responses were taken as fact and not independently verified using record review.

To analyze the outcomes and compare groups, the investigators used an intention-to-treat analysis in which they calculated incidence rate ratios and mortality rate ratios with available person-time from randomization until diagnosis/death or censoring, whichever came first. Because of the sequential enrollment using blocks of patients, the analysis was designed to account for varying rate ratios over time. Mortality rates between groups were then compared using a log-rank test.

Results. Participants in the 2 groups were similar with respect to baseline characteristics. Half were women, over 60% of patients were younger than 64 years, approximately 85% were Caucasian, and about 41% had a history of previous colorectal screening (either through FOBT [~38%] or endoscopy [~13%]). The only significant difference reported by the authors between the 2 groups at baseline was that slightly more patients in the intervention arm reported regular ASA or ibuprofen use in the year prior to screening.

Not all patients (only 83.5%) randomized to the screening arm underwent the study sigmoidoscopy. Of those who did undergo screening and who had a positive finding, diagnostic workup was performed in 80.5%. Repeat screening endoscopies were performed at 3 or 5 years as part of the trial in just over half of the intervention group. Patients were followed for a mean of 11 years after randomization, with a 93.8% response rate to the mailed annual follow-up surveys and a 99.9% rate of vital statistics gathering to within 1 year of the cut-off date (31 Dec 2009).

The primary endpoint of death due to colorectal cancer occurred at a rate of 2.9 cases per 10,000 person years in the intervention arm, compared with 3.9 cases per 10,000 person years in the usual care arm (relative risk [RR] 0.74, 95% confidence interval [CI] 0.63–0.87, $P < 0.001$). Colorectal cancer incidence was also reduced in the screening group, with a relative risk of 0.79 (95% CI 0.72–0.85, $P < 0.001$) compared to the usual care group. Although sigmoidoscopy does directly visualize the proximal colon, this reduction in incidence was true for both distal (RR 0.71, 95% CI 0.64–0.80, $P < 0.001$) and proximal lesions (RR 0.86, 95% CI 0.76–0.97, $P = 0.01$). There was, however, no mortality benefit from screening conferred to patients with proximal colon cancers. The protective effect of screening for cancer incidence and mortality was similar across age-groups, and there was a suggestion that it was stronger in men than women, though interaction P values (gender*treatment group) did not reach statistical significance ($P = 0.052$ for incidence, $P = 0.10$ for mortality).

Of the colorectal cancer patients in the intervention group, only 24% were felt to have been screening-detected diagnoses. Within those screening-detected cancers, ~83% were found in the distal colon. Also within this subgroup, cancers were likely to be detected at an earlier stage (I or II) than within those whose cancers were not found with screening. The screening procedures themselves resulted in some complications. Namely, there was a total of 22 bowel perforations (3 during initial screen and 19 during follow-up screens), and a false-positive rate for the initial screening of 20% among men and 13% among women.

Contamination of the groups by off-study endoscopies was common, with 46.5% of "usual care" patients receiving either sigmoidoscopy or colonoscopy during the initial screening period, and 48% receiving routine colonoscopy during the remaining follow-up. Furthermore, of the intervention patients, 48% also received routine colonoscopies during the follow-up period. Despite these high rates of contamination, the majority (83.3%) of screenings among the intervention patients occurred during the first

year of follow-up, compared with taking place throughout the follow-up period for the control group.

Conclusion. Screening flexible sigmoidoscopy is associated with reduced rates of overall mortality and incidence of colorectal cancer, with a particular benefit observed for distal tumors, as compared with usual care.

Commentary

The American College of Gastroenterology's most recent guidelines for CRC screening recommend colonoscopy beginning at age 50 (or 45 for African Americans) and recurring every 10 years thereafter [1]. They offer flexible sigmoidoscopy every 5 to 10 years as an alternative test, along with CT colonography [1]. Other organizations, such as the American Cancer Society, present every 5 years sigmoidoscopy and every 10 years colonoscopy as roughly equivalent screening options [2]. It is clear that screening for CRC reduces mortality, but despite these and other recommendations, there remains some uncertainty for clinicians and patients around the optimal screening strategy. Compared with colonoscopy, many providers have concerns that sigmoidoscopy fails to visualize the proximal colon, potentially resulting in missed diagnoses of lesions in that area [3]. Others argue that even colonoscopy is suboptimal for finding proximal colonic lesions, both due to the difficulty of achieving adequate prep and the flat shape of the polyps that are common to this anatomic region [3]. Further complicating matters is the fact that many patients are resistant to endoscopy due to the intensive preparation involved and the invasive nature of the procedure [4].

To test the efficacy of sigmoidoscopy, there have been several large trials in Europe, some finding a reduction in CRC incidence and mortality using this strategy [5,6], and others concluding no benefit of sigmoidoscopy compared with no screening [7].

This large, US-based randomized trial did support the notion that screening flexible sigmoidoscopy reduces both the incidence and mortality of CRC. The randomized design of the trial with intention-to-treat analysis aims to reduce the confounding by indication that is problematic with observational studies of procedures or treatment interventions. Its large size and scope are also strengths of the trial. Additionally, the research question is of high clinical importance to providers and to all adult patients. Other strengths of the trial design include the use of block randomization, which in the setting of a multicenter, multiyear trial, helps to ensure equal distribution of patients between study arms.

The primary limitation of this trial appears to be the large amount of contamination of both the intervention and control arms with off-study endoscopic procedures. Because of the contamination, it is not clear what standard was used to define "usual care," and thus there is a wide range of patient care regimens present, probably due to variability both in practice patterns of primary physicians and patient preference around CRC screening. Given that variability, it is hard to say exactly what screening sigmoidoscopy is actually being compared with in this study. One clear difference between the groups that emerged in the results section was the timing of screening. Yes, the control group ended up getting a lot of endoscopies too, but in general they got them later in follow-up than the intervention patients, so presumably had more time to develop cancerous lesions and therefore higher CRC incidence and mortality. It is safe to assume that any benefit found in this study would have been amplified had the usual care arm had lower rates of "contamination" screening, as was the case in the Norwegian study referenced in this paper [7].

The investigators make a point of stating that this screening strategy reduced the incidence of both proximal and distal CRC. Despite the statistically significant drop in proximal CRC incidence in the intervention arm, it seems odd to attribute this to screening sigmoidoscopy itself, given that these lesions would not have been visualized using that procedure. More likely, it seems possible that these proximal lesions were actually found as a result of follow-up colonoscopies done in the setting of false-positive screening sigmoidoscopies. The investigators do insinuate this by contrasting their findings to the European trials in which no benefit was conferred for proximal lesions but in which there were also much lower rates of contamination with colonoscopy.

The measure of "contamination" itself, in which a patient survey response was taken as truth, may be somewhat unreliable, particularly if patients were asked to differentiate between endoscopy types. It certainly would have been preferable to confirm off-study procedure type and findings with medical record reviews for this important subgroup of patients.

In terms of generalizing these findings to the broader US population, it is worth noting that the vast major-

ity of patients in this study (85%) were white. Given that African Americans are at higher risk of developing CRC, a study in which they were more heavily represented might be important in terms of testing the optimal screening strategy among different racial and ethnic groups.

Finally, although this study does support the use of an initial screening endoscopy, it does not inform the issue of screening intervals. Repeat screening at 3 or 5 years occurred in only about 50% of patients, and high rates of contamination with other procedures during follow up make any inferences about repeat screening intervals very difficult.

Applications for Clinical Practice

This large randomized trial of screening sigmoidoscopy for CRC showed a decreased incidence and mortality among patients in the intervention arm as compared to usual care. Although the effects of screening would likely have been stronger if the control arm had lower rates of screening, this finding does support the use of sigmoidoscopy, particularly for lesions in the distal colon. However, it does not convincingly compare sigmoidoscopy to colonoscopy, and in patients who are amenable to endoscopy, providers should continue to prioritize colonoscopy, barring further evidence to the contrary.

—Kristina Lewis, MD, MPH

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