

How Much Does Colonoscopy Reduce Colon Cancer Mortality?

What is the effectiveness of colonoscopy in reducing colorectal cancer (CRC) mortality? Because we do not have direct evidence from a randomized, controlled trial (RCT), we must rely on indirect evidence. In this issue, Baxter and colleagues' case-control study (1) raises interesting and troubling questions about how much screening colonoscopy reduces CRC mortality. The authors used a province-wide administrative database in Ontario, Canada, to identify case patients who received a diagnosis of CRC from 1996 to 2001 and died by 2003. Five randomly selected controls who did not die of CRC were matched to each case patient. Exposure to previous colonoscopy was assessed from billing claims for case patients and controls. Among 10 292 case patients, 7.0% had previous colonoscopy, whereas among 51 460 controls, 9.8% had a previous colonoscopy. The odds ratio for the association between complete colonoscopy and CRC mortality reduction was 0.33 for left-sided lesions, which suggests a large mortality reduction. However, the result was dramatically different for right-sided lesions: An odds ratio of 0.99 indicated a roughly 1% mortality reduction, which is essentially none at all.

These results raise 3 important questions. First, are the results valid enough to warrant serious consideration if the study uses a case-control design—an inherently weaker design than a RCT? Second, presuming they are valid, which reasons—especially those that might be remediable—might explain the low effectiveness for cancer in the right colon? Finally, how does this study help us fairly consider the magnitude of colonoscopy effectiveness in reducing CRC mortality?

Case-control studies are susceptible to numerous biases (2), but several features of this study's design and results suggest that the study must be taken seriously. One possible limitation is that it was impossible to tell whether colonoscopy "exposure" was for screening asymptomatic persons or for diagnosing cancer. If cancer symptoms led to colonoscopy, then colonoscopy would preferentially be associated with cancer and death from cancer, obscuring any favorable effect of screening colonoscopy on mortality. The investigators' effort to reduce this possible bias seems reasonable—they excluded persons whose cancer diagnosis occurred within 6 months of the colonoscopy, and they did sensitivity analysis to assess whether a 6-month window was appropriate. Second, it is hard to see how a fundamental bias due to the case-control design could account for the most important finding: the large discrepancy between results for the right and left colon. Finally, the degree of mortality reduction for left-sided CRC is similar to findings of a case-control study of sigmoidoscopy that used a very strong "internal control" group (3, 4) and showed a roughly 60% reduction in CRC mortality for lesions within reach of the scope (3). The results for the left colon

are also similar to findings of a nonrandomized trial from Norway showing that sigmoidoscopy (when positive and followed by colonoscopy) reduces CRC mortality by about 80% (5). These 3 considerations suggest that we must take this study's results seriously.

What might explain the lack of effectiveness of colonoscopy in the right colon? Because this study used an administrative claims database and not actual medical records, we do not have the clinical details to judge whether colon preparation may have been poor, thereby obscuring important lesions. In this Canadian practice setting, internists and surgeons, rather than gastroenterologists, did about 70% of the colonoscopies. One could speculate that differences in experience or proficiency and in the quality of the examination might explain some of the results. Another study from Ontario showed that when internists and family practice physicians did colonoscopies, they missed CRC more often than when gastroenterologists did them (6). Perhaps examinations recorded as being "complete" did not reach the cecum, or perhaps the colonoscopy withdrawal time was short, leading to an incomplete mucosal inspection and missed lesions. Quality problems, if they occurred, could be remediable.

Other reasons for poor protective effect in the right colon might be more difficult to remedy. One possible biological reason is that although adenomas and CRC may on average grow slowly, that average almost certainly comprises a spectrum of growth rates and dwell times—a spectrum whose dimensions are unknown. Screening colonoscopy could miss fast-growing neoplasms that become fatal cancer before the next colonoscopy. Simulation modeling of screening programs shows that a small proportion of rapidly growing CRCs can have a disproportionate effect on mortality and decrease the effectiveness of a screening program (7). Some evidence suggests that right-sided lesions may be more likely to be fast-growing lesions (8), but we do not know the spectrum of growth rates for either right- or left-sided lesions. Preventing CRC mortality from fast-growing lesions would require more frequent examinations, which are potentially feasible but would incur increased expense and risk. We do not know which reasons explain low efficacy in the right colon and whether they are remediable.

How do these considerations and Baxter and colleagues' study (1) help us understand the magnitude of CRC mortality reduction from colonoscopy while we wait for RCTs to provide stronger evidence? One RCT of screening colonoscopy is in the planning stages (9). Randomized, controlled trials of sigmoidoscopy in the United States (10) and the United Kingdom (11) will not report mortality results for years and then will provide answers only for the left colon. Current estimates of the effect of colonoscopy on CRC incidence—a 76% to 90% reduc-

tion—are based on an analysis of data from the NPS (National Polyp Study) (12). A major limitation of the NPS analysis is that it did not have a concurrent control group. The analysis compared CRC incidence rates among NPS participants having polypectomy with expected rates in 3 population-based, historical control groups. The problem is that some persons in the control groups might have already had CRC at baseline. Persons enrolling in the NPS had colonoscopy done (to find the polyp that defined eligibility for the study), and persons with CRC at this baseline colonoscopy were ineligible and were excluded from the NPS. In contrast, controls did not have baseline colonoscopy. Some could have had asymptomatic CRC present at baseline that, appearing later, would be counted as a new CRC (13). The NPS analysis tried to adjust for this problem, but successful adjustment requires knowledge about CRC growth rates and dwell times—facts that are not known. In light of these other studies, Baxter and colleagues' (1) results seem consistent with a CRC mortality risk reduction of about 60% to 70% for the left colon and highlight the fact that we have few data—even indirect data—about efficacy in the right colon.

These concerns and the authors' results should make us worry that we might mislead our patients (and ourselves) by saying that colonoscopy reduces the risk for CRC death by 90% (14). On the basis of considerations discussed earlier on case-control studies of sigmoidoscopy and RCTs of fecal occult blood testing (15–17) that show CRC mortality reduction after colonoscopy (done because of a positive fecal occult blood testing result), a reasonable estimate—and what we should probably tell our patients—might be closer to a 60% to 70% reduction of the risk for death from CRC with high-quality colonoscopy. A 60% to 70% mortality reduction is not as good as 90%, but it should not be considered disappointing. It would be remarkably high compared with screening for other types of cancer, such as breast (a 25% cancer mortality reduction at best) or prostate cancer (no proven cancer mortality reduction).

What we believe about colonoscopy effectiveness is not just an academic issue—it has practical consequences. If we promise too much, we risk causing problems for our patients and ourselves if any CRC that occurs after screening colonoscopy is viewed as a mistake that we must explain to a patient and perhaps to a lawyer. A goal of avoiding all deaths from colon cancer may be admirable, but we do not have evidence that we can achieve it. A mindset that “no CRC can occur on our watch” may already contribute to overutilization of colonoscopy in postpolypectomy surveillance (18). Unrealistic goals may incur risks if they cause overuse of colonoscopy. Although colonoscopy is generally safe, it is still an invasive procedure with a 0.2% rate of serious complications (13, 19)—10 times higher than for any other commonly used cancer screening test. Repeated examinations over time may incur a substantial cumulative rate of complications (13), not even counting

hard-to-detect complications (if they occur), such as silent myocardial infarction (5, 20).

Colonoscopy is an effective intervention, but as Baxter and colleagues suggest (1), we must realize that current evidence is indirect and does not support a claim of 90% effectiveness. Until we have better data, we can be grateful and optimistic to have a useful intervention to offer our patients, but we should be realistic and cautious when discussing the magnitude of both benefits and risks with them.

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