

COMMENTS AND RESPONSES

The Effectiveness of Colonoscopy in Reducing Mortality From Colorectal Cancer

TO THE EDITOR: Several issues in the article by Baxter and colleagues (1) raise concern about the adequacy of the examinations performed and therefore the clinical significance of the findings. First, the cecal intubation rates ranged from 79% to 83% among all colonoscopists. For gastroenterologists specifically, the cecal intubation rate was only 83%, which is well below current accepted rates. In subgroup analysis, the cecal intubation rate was even lower (73%) in the case patients. Baxter and colleagues appropriately performed additional subgroup analysis to compare complete versus incomplete colonoscopy in terms of cancer detection rates. However, it can be hypothesized that even if a complete colonoscopy was performed, a colonoscopist with a low cecal intubation rate may lack the experience and technical skill to adequately identify polyps, particularly flat lesions, during the examination. Supporting this is the fact that in the study, the polyp detection rate was 26% in case patients and 21% in control participants. A significant proportion of these polyps may have been hyperplastic and, therefore, the overall adenoma detection rate may have been significantly lower than the current standards in the gastroenterology literature, which suggest that adenomas be detected in 15% of women and 25% of men (2). In addition, one might expect that in this older, predominantly male case sample (54% male; median age, 73 years) in which cancer is already present, the adenoma detection rate in other parts of the colon would be even higher. In a recent study (3), fellow participation in colonoscopy yielded an adenoma detection rate of 37%, raising concern that our accepted adenoma detection rate may be too low.

On the basis of these facts, it is not surprising that the rate of missed cases of cancer was high, particularly in the right colon, and especially given that many of these lesions may have arisen from flat, subtle lesions that would be much more difficult to detect than a well-defined polyp. This study underscores the need to have all gastroenterologists strive to meet accepted rates of cecal intubation and polyp detection. The aggressive and evasive characteristics of right-sided lesions that this article seems to support also highlights the idea that careful optical colonoscopy to identify subtle mucosal changes in the right colon may be superior to “virtual” colonoscopy, which can miss flat lesions.

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TO THE EDITOR: The recent study by Baxter and colleagues (1) highlights that although colonoscopic screening decreases death rates from colon cancer, it has limitations, particularly with respect to preventing deaths from cancer of the right colon. Baxter and colleagues suggest that these limitations might reflect the technical difficulty of routinely reaching and identifying right-sided colonic lesions, which may be flat and harder to visualize or might have a different biology from more distal cancer. Indeed, it is well established, for example in the context of the Lynch syndrome, that colon cancer with microsatellite instability, which predominantly appears in the right colon, develops at an accelerated rate and can appear sometimes within 12 to 24 months of previously normal colonoscopies. The more common types of nonfamilial microsatellite instability colon cancer are also likely to easily give rise to “interval” colon cancer, appearing between screening colonoscopies.

What, then, can be done to enhance the efficacy of colon cancer screening programs? We suggest the addition of stool DNA tests between colonoscopies. These tests directly detect DNA molecules that are shed from colonic neoplasms into the stool and that bear signature molecular alterations of colonic neoplasia. Stool DNA testing, with its high sensitivity for cancer detection, has been endorsed as an acceptable option for colorectal cancer screening by the American Cancer Society/Multi-GI Society Task Force (American Gastroenterological Association, American College of Gastroenterology, American Society of GI Endoscopy) and American College of Radiology and has been included in their joint national colorectal screening guideline (2). The test is noninvasive and inexpensive and seems to be equally sensitive for detecting lesions in the right and left colon (3–5). Thus, stool DNA testing is an attractive technology for identifying persons in whom intensive examination of the right colon could be of value during an initial colonoscopy, or routinely for identifying individuals in whom a right-sided lesion develops after normal colonoscopy. Broadening routine screening to use, sequentially, a visual method (colonoscopy) complemented by an interval molecular method (stool DNA testing) could more effectively identify patients harboring active colorectal neoplasia than either approach alone.

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TO THE EDITOR: In their recent study (1), Baxter and colleagues observed that colonoscopy was associated with a significant decrease in left-sided but not right-sided colorectal cancer mortality. If data are available, it would be instructive to report differences in polypectomy rates between case patients and control participants. In the end, it is removal of premalignant polyps, rather than colonoscopy per se, that accounts for colorectal cancer prevention.

We reported elsewhere (2) our findings from a population-based study of all colorectal cancer cases in Olmsted County, Minnesota, assessing concurrent trends in colorectal cancer incidence, screen-detection, and polypectomy rates. Over the study period (1980 to 1999), polypectomies increased 4-fold and colorectal cancer incidence decreased by 23%. The decrease in colorectal cancer incidence was accounted for by a 40% reduction in left-sided colorectal cancer ($P < 0.001$), because the incidence of right-sided colorectal cancer remained essentially unchanged.

We speculated in our study that the limited impact of polypectomies on right-sided colorectal cancer incidence may have been due to a distal bias in screening, to changing host–environment factors, or to a different precursor lesion and natural history.

Although both of these retrospective population-based studies have inherent limitations, results are corroborating and raise questions about the effectiveness of currently practiced colonoscopy for right-sided colorectal cancer prevention. In light of the well-documented left-to-right shift in colorectal cancer incidence across many countries, a concerted effort is needed to better understand the biology of right-sided colorectal cancer and develop rational screening interventions.

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TO THE EDITOR: To provide information regarding the efficacy of screening colonoscopy in preventing death from colorectal cancer, Baxter and colleagues (1) analyzed administrative claims data from Ontario, Canada. Although this choice had the advantage of yielding a very large sample (10 292 deaths from colorectal cancer), it had some drawbacks that we believe seriously threaten the validity of the results obtained.

First, colonoscopy, like most screening tests for cancer, can also be used to evaluate persons who are suspected to have cancer, on the basis of symptoms or signs. Because the case patients in this case–control study all had colorectal cancer, many of them would have received colonoscopy in response to symptoms or signs. The data available to Baxter and colleagues could not distinguish between screening and diagnostic colonoscopies. To the extent that tests not screening done for were labeled as “screening,” the proportion of “screened” cases would be spuriously high, leading to a spuriously high odds ratio and thus a spuriously low estimate of screening efficacy.

Second, being cognizant of this limitation, Baxter and colleagues omitted from their analysis colonoscopies that were most likely not to represent screening (that is, tests done within 6 months of diagnosis of the person who later died of colorectal cancer and the corresponding date in their matched control participants). However, this analytical choice may produce a strong bias in the opposite direction. The problem stems from the fact that screening tests among patients with cancer and control participants during the period before the date of the patients’ diagnoses are not distributed in time in the same way. Especially for a sensitive test, such as colonoscopy, almost all screening tests performed in case patients (during the period in which the cancer is detectable by means of this test) will have been done close to the time of diagnosis. Had a screening colonoscopy been done earlier during the preclinical phase of the cancer, the tumor would have been found then. In control participants, almost all of whom do not have colorectal cancer, the distribution of screening colonoscopy during the corresponding period would have been far more uniform.

To gauge the impact of a strategy of deleting from consideration all tests done within 6 months of diagnosis, assume a perfectly sensitive screening test for cancer that, in the absence of screening, would be present for several years before its diagnosis on the basis of symptoms or signs. Assume as well that the receipt of screening by study participants can be accurately ascertained, and also that no effective treatment exists for the condition being screened for. A valid case–control study of the efficacy of the screening test, a test which failed to yield any mortality reduction, should observe an odds ratio of 1 (that is, a similar proportion of case patients and control participants with a history of screening). However, a far larger proportion of screening tests done in case patients than in control participants will be excluded in an analysis that ignores tests performed in the 6 months before the date of diagnosis, leading

to a spuriously low odds ratio and a spuriously high estimate of screening efficacy (2).

For these reasons, as well as other (probably smaller) sources of potential bias—such as failure to include all deaths from colorectal cancer that ultimately will occur among persons diagnosed in the study population during 1992 to 2001 (3), or confounding by family history and other risk factors—the odds ratios obtained by Baxter and colleagues may well not be indicative of the actual impact of screening colonoscopy on mortality from colorectal cancer. We agree with Baxter and colleagues, and with the opinion expressed in the accompanying editorial (4), that colonoscopy may have greater efficacy in the prevention of death from distal than proximal colorectal cancer. However, we believe it would be fortuitous if the efficacy of colonoscopy estimated by Baxter and colleagues against mortality from either distal or proximal colorectal cancer corresponded to the true value.

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TO THE EDITOR: In their recent study (1), Baxter and colleagues do not discuss what sedation, if any, the patients received. Although the study took place in Canada, it has become increasingly common in the United States for a separate anesthesia care provider to be present during colonoscopies both to ensure the safety of the patient and to provide a deeper level of sedation. This deeper level of sedation presumably provides the endoscopist a better opportunity for conducting a thorough examination, especially in the right side of the colon. The fact that about 70% of the procedures were performed by surgeons and internists leads one to suspect that a separate anesthesia provider was not present for many of these procedures and that optimal sedation was not achieved. The poor tolerance of colonoscopies in inadequately sedated patients may be reflected in the relatively low cecal intubation rates and the inability to examine the right side of the colon sufficiently well to affect mortality rates.

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TO THE EDITOR: We read with interest the recent article by Baxter and colleagues (1). This landmark article demonstrated a clear benefit of colonoscopy for left-sided colorectal cancer but failed to show any survival benefit for right-sided colorectal cancer. Plausible explanations for this important observation include unique tumor biology for a subset of right-sided colorectal cancer and technical factors resulting in missed right-sided colorectal cancer by colonoscopy. In fact, an alternate cancer pathway distinct from the typical adenoma–carcinoma sequence—the serrated polyp pathway—has been identified. The serrated polyp pathway is a predominately right-sided process and may account for 15% of sporadic colorectal cancer. However, the precursor serrated lesion is typically large and seems to have a very long dwell time, suggesting that neither cancer prevention nor detection should be diminished. No convincing evidence exists for a rapidly progressive or de novo sporadic colorectal cancer that favors the proximal colon. This leaves missed right-sided cancer at colonoscopy as the most likely explanation.

It stands to reason that proximal colonic tumors that are farther from the anus would pose a greater diagnostic challenge for colonoscopy. Several interrelated factors probably limit colonoscopic detection of right-sided pathology: the proximal aspect of right-sided colonic folds represents a recognized blind spot for physical endoscopy (2, 3); suboptimal bowel preparation tends to obscure the right colon to a greater degree; incomplete examination (whether recognized or not); and the presence of flat lesions, which are particularly vulnerable to the first 2 limitations. In contrast, computed tomographic colonography has distinct advantages for right-sided evaluation, including the absence of physical directional constraints, allowing complete evaluation; relative ease of distention of the proximal colon; the ability to tag residual stool with oral contrast; and combined 3-dimensional and 2-dimensional assessment for flat lesions. This may help explain the striking differences observed in colorectal cancer detection between primary computed tomographic colonography and colonoscopy.

In our comparison trial (4), 8 cases of right-sided cancer were found in the computed tomographic colonography screening cohort, versus just 1 in the closely matched colonoscopy group. In a Mayo Clinic validation trial (5), 4 of 5 cases of cancer (80%) were missed at initial colonoscopy, despite serving as the reference standard for computed tomographic colonography, which prospectively detected all 5 cases of cancer. With a priori knowledge of computed tomographic colonography–detected lesions, the miss rate of colonoscopy is considerably lower. Perhaps a primary screening strategy that alternates between flexible sigmoidoscopy and computed tomographic colonography would optimize cancer detection and minimize invasiveness.

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TO THE EDITOR: Baxter and colleagues (1) concluded that the effect of colonoscopy on death from colon cancer (particularly right-sided disease) was weaker than previously thought. However, we feel the study design introduced significant bias, specifically in terms of the definition of control participants. Had the outcome been development of colon cancer (rather than death from colon cancer), elimination of patients with nonfatal colon cancer from the control group would have been appropriate. However, because the study outcome was death, only patients who died of colon cancer should have been excluded from the control group, regardless of whether persons with past cancer were excluded from being case patients (2–4). Patients diagnosed with colonoscopy early enough to have prevented death should have been allowed to be “noncase patients,” because they did not die of colon cancer (2–4). Exclusion of even a small proportion of these patients, almost all of whom would have undergone colonoscopy, probably dropped the control colonoscopy exposure by a few percent. Each percent change corresponds to a 0.1 difference in the odds ratio, because the baseline exposure rate was only 9.8% (1). Furthermore, should the rate of detecting nonfatal colon cancer with colonoscopy differ for right-sided cancer, this could differentially bias the right-sided odds ratio, explaining in part the surprising lack of apparent benefit in that group.

Although the above is by far the most important (and clinically significant) potential bias, lack of adjustment for flexible sigmoidoscopy (known confounder, associated with reduced mortality and with exposure to colonoscopy), family history (associated with cancer

and colonoscopy) and preparation quality (particularly for the right colon) may have introduced bias.

Other issues include the age range chosen. Indeed, deaths at age 50 years are not expected to be affected by screening colonoscopy, which is recommended for most persons older than 50 years, and may not affect mortality for years afterward. Similarly, the upper age of 90 years included deaths 15 to 20 years after screening generally stopped. This dilutes estimates of screening effectiveness. Finally, inpatient colonoscopy is generally performed for symptoms, rather than for screening; lack of adjustment for inpatient status reduces the apparent benefit of screening outpatient colonoscopy.

Inpatient colonoscopies may have poorer visualization (especially of right-sided disease), such as in the context of bleeding, which may again bias the results toward the null (lower apparent benefit).

These methodological concerns have probably contributed to underestimation (by a clinically significant magnitude) of the benefits of colonoscopy in general, and in the right colon in particular. Further data are required to support the claimed overall and site-specific conclusions.

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IN RESPONSE: Our recent study investigating the association between colonoscopy and colorectal cancer mortality has generated substantial interest. The media attention in response to publication of our study has been due, at least in part, to a misinterpretation of our methodology and primary outcome. We did not evaluate the rate of missed cancer cases at colonoscopy, and the degree to which missed cancer cases (or missed precursor lesions) may have contributed to our findings—that colonoscopy is significantly associated with a reduction in mortality from left-sided colorectal cancer but not right-sided colorectal cancer—is unknown. There has been considerable speculation with respect to the influence of procedural quality in Ontario on our findings; however, our understanding of the quality of colonoscopy in the general population in any jurisdiction

tion is limited and is almost certainly lower than that published in series from expert centers.

In addition, this line of argument reveals an unwavering belief in the potential of colonoscopy to prevent the overwhelming majority of colorectal cancer cases and colorectal cancer deaths. However, our understanding of the molecular basis of colorectal cancer carcinogenesis is evolving, and it seems likely that a considerable proportion of cancer cases do not originate from easily identified adenomas that have a slow rate of progression (1). Although improvements in the quality of colonoscopy and the use of other screening methods may increase our ability to detect colorectal cancer or precursor lesions (such as the serrated adenoma), a rigorous evaluation of the relative effectiveness of colorectal cancer screening methods in a randomized trial is needed. Specifically, we need to know the marginal benefit of colorectal cancer screening with colonoscopy compared with flexible sigmoidoscopy in terms of reducing deaths from this disease.

Case-control studies are a challenging methodology and prone to numerous biases. We agree with Dr. Romagnuolo and colleagues that selection of case patients and control participants is important and can be difficult, particularly in evaluation of maneuvers that may have a role in screening, investigation of symptoms, and surveillance of patients after treatment. We did not include control participants in whom colorectal cancer was diagnosed before the date of diagnosis of their matched case patient because the appropriate exposure interval in such individuals is unclear, given that most would be undergoing regular surveillance colonoscopy after diagnosis. Because exposure in our study was based on administrative data, our information on exposure to colonoscopy was complete for all case patients and control participants and accurate with respect to timing, necessary prerequisites to minimize bias when only those without disease are selected as control participants (2). The length of follow-up after diagnosis might be considered too short to ensure that enough time had elapsed after diagnosis to identify all cases (that is, all colorectal cancer deaths in those with colorectal cancer diagnosed in our study interval); however, this would tend to bias the study toward an overestimate of the strength of the association between colonoscopy and mortality from colorectal cancer.

Far more important in terms of threat to the validity of our study results, we could not determine the indication for colonoscopy necessitating the use of an exclusion window, in which colonoscopy performed close to the date of diagnosis (whether for screening or investigation of symptoms) was not considered an exposure. We agree with Drs. Weiss and Doria-Rose that, because of this, it would

be ill-advised to consider our odds ratio estimates of the association between colonoscopy and colorectal cancer death as precise or generalizable to other populations. Although many assume that the limitations of our study have resulted in an underestimate of the strength of the association between colonoscopy and colorectal cancer mortality, Drs. Weiss and Doria-Rose correctly highlight that, because of the necessity of the 6-month exclusion window, our study may have overestimated the strength of the association. However, despite the limitations, there is no reason to conclude that potential biases due to the study design would have influenced the major findings of this study: that colonoscopy is strongly associated with a reduction in colorectal cancer mortality, but that the association is not uniform throughout the colon. Although our study does not provide an explanation for the lack of association between colonoscopy and prevention of right-sided colorectal cancer deaths, our findings seem to be consistent with an emerging literature (3–5).

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