What Don’t We Know About Colonoscopy? New Study Raises Questions About Practice, Biology, and More

By Renee Twombly

The sanguine attitude that many physicians and most other people have about colonoscopy—it may not be fun, but the screening ensures that you won’t die from colon cancer—needs to be revised in light of recent findings from a Canadian study, say some leading U.S. gastroenterologists.

The study offered two surprises. Researchers in Toronto found that although a history of colonoscopy appeared to be associated with a lower risk of death from colorectal cancer, the drop was not as dramatic as has been assumed. Physicians have long told their patients that the screening procedure probably prevents 90% of colon cancer incidence—suggesting by inference that the mortality reduction could be as high. But this study found that roughly 67% of deaths were prevented.

And that is an important finding, because the study, published in the January 6 issue of the Annals of Internal Medicine, is the first population-based, case-control study of colonoscopy to look at mortality reduction. No randomized mortality studies have been carried out to date; the landmark National Polyp Study looked only at colon cancer incidence in people screened with a colonoscopy.

But even more surprising was the finding that the reduction in death was only from cancers detected in the left side of the colon. The death rate from right-sided colon tumors was the same whether or not a person had a colonoscopy.

“There certainly seems to be a dramatic difference between the effectiveness of colonoscopy for prevention of mortality on the left side versus the right side,” said the study’s lead researcher, Nancy Baxter, M.D., a colorectal surgeon and researcher at St. Michael’s Hospital and an investigator at the Institute for Clinical and Evaluative Sciences. “That’s not to say that colonoscopies don’t find colorectal cancers. It clearly finds cancers on the right side,” Baxter said. “It just doesn’t seem to prevent colorectal cancer deaths on the right side.”

Whereas some gastroenterologists who perform colonoscopies complained that the study was flawed, others said that the findings raised important questions and should, at least, be seen as a wake-up call for physicians who perform these tests.

“What this article basically does is it shakes people by the collar and asks, ‘What do we really know about how much colonoscopy reduces mortality?’ And the bottom line is that we don’t really know,” said gastroenterologist David Ransohoff, M.D., a professor of medicine at the University of North Carolina, Chapel Hill.

He and others say that the study raises questions about how well colonoscopy is performed in the real world, about the technologies used, and about possible biological differences between the right and left colon.

One of the most immediate questions is what physicians should tell their patients. Ransohoff, who wrote an editorial that accompanied Baxter’s findings, said that doctors should no longer say that colon cancer is likely to reduce 90% of colon cancer deaths, but they should revise that estimate down to 60%–70%. “For a screening test, that is an enormous benefit, almost better than any other kind of screening test by far,” he said. “This is still very good news.”

Baxter said that it is important that people understand the limitations of a colonoscopy. “There’s virtually no screening test that’s more invasive than colonoscopy. It’s also associated with a small risk, but a known risk, of morbidity and mortality,” she said. “So I think that when you’re discussing something with those kinds of risks, I think it’s very important that we’re completely transparent and clear about what the benefits are.”

Skill Matters

The researchers studied colonoscopies performed throughout Ontario between 1996 and 2001, hypothesizing that it would be associated with fewer deaths from colorectal cancer but might be considerably less effective in “real world” practice than had been reported in published studies.

Using administrative data from the Ontario Cancer Registry, they identify 10,292 colorectal cancer patients diagnosed between 1996 and 2003 who had died of colorectal cancer by 2003. They used other databases, such as billing claims, to select a control population of 51,460 people who did not die from the disease. To do this, the researchers randomly matched each patient with five control individuals by age, sex, geographic location, and socioeconomic status.

Within these groups, 719 patients (7%) and 5,031 control subjects (9.8%) had undergone colonoscopy. The researchers
measured the odds of exposure to colonoscopy in colorectal cancer patients who died from the disease and in control subjects who did not die of the cancer to estimate the association between colonoscopy and death from colorectal cancer. The odds ratio for the association between a completed colonoscopy and reduction of death from colorectal cancer was 0.33 for left-sided lesions but 0.99 for right-sided lesions—a reduction of about 1%.

Baxter admits that the study design is complicated and that this “has definitely confused a lot of people.” She said it also has limitations, including the fact that researchers did not know why colonoscopies were ordered for those who had them. Screening colonoscopies “were probably in the minority,” she said, which suggests that the test may have been conducted because of worrisome symptoms. “In those cases, some may not have been effective in preventing cancer deaths.”

But some investigators say that there are a variety of other reasons that colonoscopy was not as effective as expected. One could be the proficiency of physicians performing the procedure, said Carl Jaffe, M.D., a professor at Boston University and former chief of the National Cancer Institute's Diagnostic Imaging Branch. Gastroenterologists performed only 30% of colonoscopies in the Canadian study (surgeons performed 40% and internists did the rest). In the United States, however, gastroenterologists, who specialize in colonoscopies, perform most of these procedures, Jaffe said. “Skill matters in optical colonoscopy, and the results of this study could all be explained because of it.”

Michael Wallace, M.D., a professor of medicine at the Mayo Clinic in Florida, agrees that it appears the quality of colonoscopy in the study could be an issue. He noted that the rate at which the Canadian clinicians reached the cecum, the colon’s junction with the small intestine, was only 70%. That finding suggests that some cancerous polyps may have been missed in the right colon, the area that extends from the cecum through the ascending colon to the beginning of the transverse colon. Contributing to this problem may be the endoscope technology used in the 1990s, Wallace said. The older instruments were less sensitive than instruments used today in picking up flat or serrated lesions, which are harder to see than the standard mushroom-shaped polyps.

Another factor may be the amount of time spent on the procedure. In a colonoscopy, a physician extends a scope through the floppy, twisted colon to the cecum and then pulls slowly back to examine the entire colon for polyps. The Canadian study did not include any information on how long it took clinicians to perform the procedure, which is understandable, Wallace said. But a recent evaluation of time spent on these procedures, published in 2006 in the New England Journal of Medicine, demonstrated that performing the screening in less than 6 minutes reduces detection of polyps. “We have data to show we need to take our time, but that wasn’t as well recognized during the time frame of the Canadian study,” Wallace said.

But those problems still exist, even among specialists, said Douglas Rex, M.D., professor of medicine at Indiana University School of Medicine in Indianapolis. “We’ve got study after study showing that there’s huge variation between gastroenterologists in how effectively they find adenomas,” he said. “Low-quality colonoscopy is not very effective at all. And there are people doing colonoscopy who are so ineffective at it that it would be just better if they weren’t doing it.”

Another potential explanation for the lack of mortality reduction in the right colon in the Canadian study is the way people prepare for the procedure, said Rex. Most people use bowel preparations the night before, but by the time of the colonoscopy, a layer of intestinal secretion can obscure part of the right colon. Using half of the cleansing dose the morning of the colonoscopy solves that problem, Rex said.

“This test has to be done with high quality. It has to be done with an effective preparation. It has to be done by somebody who is trained in doing careful, obsessive–compulsive examination of the colon and is looking for subtle lesions in the colon, and [it] has to be done with effective bowel preparation,” he said.

**Biological Differences?**

However, Baxter does not agree that skill or technology is the whole issue because these factors could not account for the dramatic difference seen in colon cancer mortality between the left and right colons—a discrepancy that some other studies have noted.

What intrigues her most is the question of whether the two sides of the colon produce cancer in distinct ways. “There may be a greater number of cancers that don’t develop through a polyp-to-cancer sequence on the right than on the left,” she said.

The two sides of the colon are distinct, Baxter said, because they derive from different embryonic structures. The right side develops from the midgut and the left side comes from the hindgut. “There may be actually true biologic differences in polyp progression, and it could be that screening failed to find the polyps that were destined to progress to cancer or didn’t find the right-sided cancers early enough to change the natural history of the tumor,” she said.
“So there may be a limit to how effective colonoscopy will be in terms of preventing right-sided colorectal cancer deaths.”

Roy Soetikno, M.D., agrees with her that there seem to be differences between lesions that lead to colon cancer development. He has found that the flat and slightly depressed lesions in the colon—the “nonpolypoid” kind that are very hard to see in a typical colonoscopy—are more aggressive. “When you find them, they have a higher chance to be invasive carcinomas,” said Soetikno, a gastroenterologist at the Veterans Affairs Palo Alto Health Care System in California.

These lesions are also found in the stomach, and they are routinely detected by Japanese specialists who annually screen many Japanese for early gastric cancer, which is a leading cancer killer in that country. These physicians find many flat lesions, Soetikno said. Although this was believed to be an ethnic characteristic, Soetikno wanted to be sure that people in the U.S. did not develop the same aggressive nonpolypoid neoplasms, so he invited Japanese specialists to screen a population of 1,819 patients undergoing elective colonoscopy from 2003 to 2004.

In the March 5, 2008, issue of *JAMA*, Soetikno describes how the physicians, using blue dye to highlight the flat lesions with their specialized endoscopes, found that the flat or depressed lesions accounted for 15% of neoplasms, which contributed to 54% of cancers that were detected.

“Everyone was surprised, because the U.S. population is not supposed to have these particular lesions,” Soetikno said. “We think existence of these flat or depressed lesions is one of the potential reasons why we have not been able to push down mortality from colon cancer.” He added, however, that these aggressive lesions were found throughout the colon in patients he studied. “Whether it is hard to find on the right side, I just don’t know,” he said.

Other institutions are now using more advanced forms of endoscopy to look for these flat lesions. The Mayo Clinic, for example, is testing use of high-definition endoscopes with special filters to highlight flat lesions. “With this technology, we substantially reduced the rate by which we missed these lesions,” said Wallace.

Increased interest in such technologies and other ways to improve colonoscopy seems one likely result of the Canadian study. “It’s important that we understand that colonoscopy isn’t perfect, and hopefully this study will push people to really achieve high-quality colonoscopy,” Baxter said.