

Colorectal cancer screening lacks evidence of benefit

PAUL MOAYYEDI, BSc, MB ChB, PhD, MPH, FRCP, FRCPC*

AstraZeneca/Richard Hunt Chair of Gastroenterology, Head, Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada

ABSTRACT

Although some studies indicate that screening with fecal occult blood testing or colonoscopy prevents deaths from colorectal cancer, the benefits may be offset by more deaths from other causes. Whether this phenomenon is due to anxiety, test bias, or merely chance, more evidence is needed; widespread screening in the general population is premature.

SCREENING for colorectal cancer is widely accepted and practiced in the United States and Canada, but is it justified on the basis of the standards of evidence-based medicine?

This article evaluates whether colorectal cancer screening with fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy actually saves lives, and it discusses issues in mammography as an analogous example of the questionable value of widespread screening programs.

FECAL OCCULT BLOOD TESTING: DOES IT SAVE LIVES?

Fecal occult blood testing has been used as a screening tool for about 25 years, and a lot of evidence has been gathered to evaluate its efficacy.

Towler et al¹ reviewed four randomized trials²⁻⁵ that included a total of nearly 330,000

people in Europe and the United States who were followed for about 9 years. People assigned to screening had a 16% lower mortality rate from colorectal cancer than those not assigned to screening. Moreover, those who actually were screened (not everyone who was assigned to screening actually followed through) had a 23% lower mortality rate from colorectal cancer than those not assigned to screening. Although not every study showed a statistically significant benefit from screening, the combined data did.⁶

Achkar and I⁷ analyzed the all-cause mortality rates in three of the four studies that Towler examined^{2,8,9} (the fourth study did not provide the relevant data). Nearly 250,000 people were included, of whom more than 2,000 developed colorectal cancer during the 11 to 18 years of follow-up at that point. We found that the screened groups had significant fewer deaths from colorectal cancer, but this benefit was balanced by slightly more deaths from causes other than cancer, although no single particular cause of death was increased. Overall, we found no statistically significant impact on the overall death rate.

To look at this issue another way, one can compare the benefits and harms of screening. In these studies, screening prevented an estimated 237 colon cancer deaths to date; to prevent a single death, 667 people needed to be screened. On the other hand, 465 extra deaths occurred from causes other than colorectal cancer; to produce one of these extra deaths, only 400 people needed to be screened.

What could cause the observed increased death rate from other causes?

Chance. The *P* value for the increased rate of death from noncancer causes in our study was

The value of screening is hard to assess, especially if gains are small

*Dr. Moayyedi has disclosed that he has received honoraria and consulting fees from the AstraZeneca and Janssen-Ortho corporations, and that AstraZeneca partly funds his endowed chair through an unrestricted donation.

.03, which is statistically significant, but just barely.¹⁰ In addition, after our study was published, Hewitson et al¹¹ reanalyzed the data using unpublished data obtained from the fourth study and found that although there were still more deaths from causes other than colorectal cancer in the screened group, the difference was no longer statistically significant.

Substitution of other causes of death. Because everyone dies from something, preventing deaths from one disease means that the number of deaths from other causes must increase. But the expected background mortality rate among the screened patients who were estimated to have avoided dying of colorectal cancer did not account for all of the extra deaths.

Reporting bias. Randomized controlled trials of screening programs cannot be conducted in a double-blind fashion. The subjects know which group they are in, which may influence how they behave during clinical evaluations; they may even reveal their screening status to their doctors. Bias can be of particular concern when a physician reports the cause of death: a doctor who knows a patient is in a study and is uncertain of the actual cause of death may be reluctant to attribute it to the targeted disease.

Screening might cause harm. Although the fecal occult blood test cannot directly cause physical harm, whether psychological effects of screening are important is worth further study. Because such a large population is screened, even small effects could have a significant impact.

For example, people who are screened may feel “safe” and adopt a riskier lifestyle.¹² It is difficult to know if this phenomenon actually occurs: it has been evaluated for screening with flexible sigmoidoscopy for colorectal cancer and found not to be the case.

Screening causes anxiety

Screening causes anxiety: although the test itself probably provokes only minor anxiety, a positive result that needs follow-up can be very upsetting. Most data on this subject have been from breast cancer screening with mammography.

Barton et al¹³ found that women scored increasingly higher on an anxiety assessment

scale if they were told they needed, respectively, repeat mammography because of an inadequate initial study, follow-up mammography in 6 months, ultrasonography, or a biopsy. Although average anxiety levels for each group were subclinical to mild, some women had levels consistent with posttraumatic stress disorder.

Anxiety may be insignificant if it is short-lived, as one might predict for false-positive test results. But Brett and Austoker¹⁴ found that women who had false-positive mammography results had persistent anxiety for at least 3 years after having been given a clear result following fine-needle biopsy, a 6-month early recall appointment, or surgical biopsy.

■ FLEXIBLE SIGMOIDOSCOPY: RESULTS NOT YET IN

Flexible sigmoidoscopy offers several advantages over colonoscopy as a screening test for colorectal cancer: about one third of the colon can be evaluated (the area in which more than half of colorectal cancers arise), preparation is less rigorous, the procedure is less invasive, and it costs less.

Three randomized trials involving 360,000 subjects are being conducted, with about 6 years of follow-up. The colorectal cancer mortality rates have not yet been reported.

■ COLONOSCOPY: DATA NOT OPTIMAL

Colonoscopy is the preferred screening test for colorectal cancer in the United States and some European countries. Compared with fecal occult blood testing, it gives fewer false-negative results, and it is likely to detect cancer earlier. Most importantly, polyps—which give rise to up to 90% of colon cancers—can be removed during the procedure, so the test may help prevent cancer rather than only detect it.

In theory, randomized controlled studies of screening colonoscopy should show more benefit than that seen with fecal occult blood testing. However, no randomized controlled trials have been published. One pilot study is being conducted in the United States but does not include enough subjects to be able to show

Anxiety from screening may have an impact on health in a large population

statistically significant effects on rates of death from colorectal cancer.

Observational studies show benefit

Several case-control studies have been done, however.

Winawer et al¹⁵ analyzed data from the National Polyp Study, in which 1,418 patients underwent complete colonoscopy and had one or more adenomas of the colon or rectum removed. After an average follow-up of nearly 6 years, the standardized incidence ratio in the treatment group was found to be 0.24 compared with patients in three reference groups: two groups of patients who did not have polyps removed and a general population registry. (A standardized incidence ratio of 1.0 indicates that the occurrence of an event is the same in two groups; less than 1.0 indicates that there is a lower incidence in the experimental group.)

This study had a serious flaw: the chosen comparison groups introduced a bias in favor of the treatment group. Although the general population registry (the National Polyp Study) uses a population in the United States, one of the other comparison groups was from England. In addition, people who attend screening and surveillance tend to have lower death rates from cancer and should not be compared with the general population. An analysis using fairer comparison groups would probably have resulted in a less impressive standardized incidence ratio.

Muller and Sonnenberg¹⁶ performed a case-control study in nearly 33,000 veterans and found a significantly lower risk of colorectal cancer for at least 6 years following colonoscopy. Sigmoidoscopy was also found to be effective, but less so.

In another case-control study, Singh et al¹⁷ evaluated more than 32,000 people in a Manitoba database who underwent colonoscopy and were found to have no colorectal neoplasia. Compared with the general population, they had a significantly lower incidence of colorectal cancer for the 10 years of the study.

Observational studies are not definitive

Although the observational studies above support the use of colonoscopy as a screening

test, randomized, controlled trials remain the gold standard in determining the value of an intervention. Promising findings in epidemiologic studies do not always hold up in randomized controlled trials.

A good example of the problem with relying on case-control studies is evaluating the role of fiber intake on colorectal cancer incidence. Howe et al¹⁸ evaluated 13 case-control studies that looked at whether fiber intake has an effect on the incidence of colorectal cancer. The combined data indicated that high fiber intake is associated with a 50% lower incidence of disease.

These promising findings prompted several randomized controlled studies that involved supplementing dietary fiber in people who were at increased risk for colorectal cancer. Asano and McLeod¹⁹ did a meta-analysis of five randomized controlled trials involving more than 3,500 patients who were under colorectal polyp surveillance and found no difference in the incidence of adenomas between the intervention and control groups.

Does removing adenomas reduce colorectal cancer risk?

To assess the impact of polypectomy on colorectal cancer risk, I examined data from three Cochrane reviews, involving seven trials and more than 8,000 patient-years of follow-up (2 to 4 years for each patient). To assess the natural course of patients with a history of adenoma removal, subjects from placebo groups in dietary intervention trials involving polyp surveillance were studied. Adenomas of all sizes recurred at an annual rate of 12%. The adenomas likeliest to develop cancer—those larger than 1 cm—recurred at a rate of 2% per year. Colorectal cancer developed at an annual rate of 0.14%. Databases of the general population for this age group show that the rate of developing colorectal cancer is nearly identical.

This finding—that patients who have already undergone polypectomy develop colorectal cancer at the same rate as the general population—can be interpreted in one of two ways. Perhaps people with adenomas start with a higher risk of developing colorectal cancer than the general population, and polypectomy and surveillance reduce their

Epidemiologic evidence does not always hold up in randomized controlled trials

risk to the normal background rate. Or perhaps screening is irrelevant, and polyp surveillance makes no difference in altering the risk of developing colorectal cancer.

■ ANALOGIES FROM BREAST CANCER SCREENING

Breast cancer screening is more established than colorectal cancer screening and entails many analogous issues. In the United Kingdom, about 1.5 million women are screened each year, and 14 million women have been screened since the program started.

As with colorectal cancer screening, the popularity of breast cancer screening is based on many trials that showed a reduction in breast cancer death rates in long-term follow-up. But when all-cause mortality is assessed, the benefits of screening disappear.²⁰ And when only high-quality trials are evaluated, no impact on breast cancer mortality rates is found. Not surprisingly, these findings created a considerable stir when first released.²¹

Screening is costly

Breast cancer screening is financially and emotionally costly. The United Kingdom spends about \$100 million annually on breast cancer screening. Each year, an estimated 200,000 women experience severe physical discomfort from mammography, and 150,000 experience anxiety.

Legal costs are also important. Missing a detectable cancer on a screening mammogram is the leading cause of medical litigation in the United States. According to 2002 data from the Physician Insurers Association of America, 30,000 lawsuits occurred, half of which were unsuccessful and 40% of which

were settled out of court. The 10% that were successful involved a mean award of \$438,000, with an estimated cost to society of \$1.3 billion annually. Although some of that money goes to patients with breast cancer, much of it goes to lawyers.

■ IS COLORECTAL CANCER SCREENING JUSTIFIED?

Since colorectal cancer screening is so costly to society, it is worth asking who benefits. Lawyers definitely benefit, as likely do gastroenterologists since they conduct more colonoscopies. Whether patients receive a net health benefit is still uncertain.

When treating patients with symptoms, clinicians use the best evidence available to them. If the evidence is weak, the clinician usually has to try something, so it is reasonable to treat patients even if you are unsure of the efficacy of the management strategy.

The situation with screening for cancer, however, raises some different ethical issues. Here we are treating the well population, and I would argue that we need stronger evidence before asking people to participate in screening. Guidelines on colorectal cancer screening from the United States, Canada, and the United Kingdom are reasonable, as they all call for more evaluation of different screening methods. Despite this call for more research, we have only one pilot randomized controlled trial and a modest amount of rigorous observational data on the effectiveness of screening colonoscopy. Whilst screening colonoscopy has the potential to reduce colorectal cancer mortality, we must collect more evidence before recommending this unreservedly to the general population. ■

■ REFERENCES

1. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. *BMJ* 1998; 317:559-565.
2. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; 328:1365-1371. Erratum in: *N Engl J Med* 1993; 329:672.
3. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; 348:1472-1477.
4. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; 348:1467-1471.
5. Kewenter J, Brevinge H, Engaras B, Haglund E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. *Scand J Gastroenterol* 1994; 29:468-473.
6. Towler BP, Irwig L, Glasziou P, Weller D, Kewenter J. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev*

Some costs of screening: health resources, discomfort, anxiety, litigation

- 2000; 2:CD001216.
7. **Moayyedi P, Achkar E.** Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. *Am J Gastroenterol* 2006; 101:380–384.
 8. **Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD.** Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002; 50:840–844.
 9. **Jorgensen OD, Kronborg O, Fenger C.** A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 2002; 50:29–32.
 10. **Moayyedi P, Achkar E.** Response to Zappa and colleagues. *Am J Gastroenterol* 2006; 101:2433–2434.
 11. **Hewitson P, Glasziou P, Irwig L, Towler B, Watson E.** Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007; 1:CD001216.
 12. **Stewart-Brown S, Farmer A.** Screening could seriously damage your health. *BMJ* 1997; 314:533–534.
 13. **Barton MB, Morley DS, Moore S, et al.** Decreasing women's anxieties after abnormal mammograms: a controlled trial. *J Natl Cancer Inst* 2004; 96:529–538.
 14. **Brett J, Austoker J.** Women who are recalled for further investigation for breast screening: psychological consequences 3 years after recall and factors affecting re-attendance. *J Public Health Med* 2001; 23:292–300.
 15. **Winawer SJ, Zauber AG, Ho MN, et al.** Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; 329:1977–1981.
 16. **Muller AD, Sonnenberg A.** Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. *Ann Intern Med* 1995; 123:904–910.
 17. **Singh H, Turner D, Xue L, Targownik LE, Bernstein CN.** Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA* 2006; 295:2366–2373.
 18. **Howe GR, Benito E, Castelleto R, et al.** Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992; 84:1887–1896.
 19. **Asano T, McLeod RS.** Dietary fibre for the prevention of colorectal adenomas and carcinomas. *Cochrane Database Syst Rev* 2002; 2:CD003430.
 20. **Olsen O, Gotzsche PC.** Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2001; 4:CD001877.
 21. **Mayor S.** Row over breast cancer screening shows that scientists bring "some subjectivity into their work." *BMJ* 2001; 323:956.

ADDRESS: Paul Moayyedi, Department of Medicine, Division of Gastroenterology, McMaster University Medical Centre, 1200 Main Street West, HSC 4W8B, Hamilton, Ontario L8N 3Z5, Canada; e-mail moayyep@mcmaster.ca.