

# Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colorectal Surgeons, and the American Society of Colon and Rectal Surgeons Evidence Based Reviews in Surgery – Colorectal Surgery

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The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients.”<sup>1</sup> The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding and reading all of the medical literature is impossible for an individual clinician. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so they can determine the validity, reliability, credibility and utility of individual articles, ie, critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled “Evidence Based Reviews in Surgery” (EBRS), supported by an educational grant from Ethicon Endo Surgery Inc, and Ethicon Endo Surgery Canada. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. EBRS has a module covering topics in colorectal surgery. Each academic year, 6 clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery but also to cover a spectrum of methodological issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, quantifying dis-

ease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery-Colorectal Surgery (EBRS-CRS) Web site. In addition, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) can access EBRS-CRS through the Canadian Association of General Surgeons Web site ([www.cags-accg.ca](http://www.cags-accg.ca)), the American College of Surgeons Web site ([www.facs.org/education/ebrs.html](http://www.facs.org/education/ebrs.html)), the Canadian Society of Colon and Rectal Surgeons (CSRCS) Web site ([www.cscr.ca](http://www.cscr.ca)), and the American Society of Colon and Rectal Surgeons (ASCRS) Web site ([www.fascrs.org](http://www.fascrs.org)). All journal articles and reviews are available electronically through the Web site. Surgeons who participate in the monthly packages can receive 6 CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple-choice questions each month. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSRCS, and ASCRS Web sites or should email the administrative coordinator, Marg McKenzie at [mmckenzie@mtsinai.on.ca](mailto:mmckenzie@mtsinai.on.ca)

In addition to making the reviews available through the CAGS and the ACS Web sites, a condensed version of the reviews will be published in the *Diseases of the Colon & Rectum*. EBRS is useful in improving your critical appraisal skills, keeping abreast of new developments in colorectal surgery, and, most importantly, you are able to obtain 6 CME credits each month from anywhere that you have access to a computer. Comments about EBRS may be directed to [mmckenzie@mtsinai.on.ca](mailto:mmckenzie@mtsinai.on.ca)

**SELECTED ARTICLE**

Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomized controlled trial. *Lancet*. 2010;375:1624–1633.

**QUESTION:** Does once-only screening flexible sigmoidoscopy at between 55 and 64 years of age decrease colorectal cancer incidence and mortality?

**DESIGN:** This is a multicenter, randomized controlled trial.

**SETTING:** This study was conducted at 14 sites in United Kingdom: 11 in England, 2 in Wales, and 1 in Scotland

**PATIENTS:** Eligible patients who indicated on a mailed questionnaire that they would take an offer of screening were randomly assigned to flexible sigmoidoscopy ( $n = 57,237$ ) or to the control group ( $n = 113,195$ ).

**INTERVENTION:** Participants randomly assigned to screening were offered an appointment for flexible sigmoidoscopy. Those in the control group were not contacted.

**MAIN OUTCOME MEASURE:** Incidence of colorectal cancer and mortality from cancer were the primary outcomes measured.

**RESULTS:** Forty thousand six hundred seventy-four (71%) people randomly assigned to the intervention group underwent flexible sigmoidoscopy. During screening and median follow-up of 11.2 years (interquartile range, 10.7–11.9), 2524 participants were diagnosed with colorectal cancer (1818 in the control group vs 706 in the intervention group) and 20,543 died (13,768 vs 6775), of whom 727 were certified to have died of colorectal cancer (538 vs 189). In the intention-to-treat analyses, colorectal cancer incidence in the intervention group was reduced by 23% (HR, 0.77; 95% CI, 0.70–0.84) and mortality by 43% (HR, 0.57; 95% CI, 0.45–0.72). The incidence of distal colorectal cancer (rectum and sigmoid colon) was reduced by 50% (HR, 0.50; 95% CI, 0.42–0.59). The numbers needed to be screened to prevent 1 colorectal cancer diagnosis or death, by the end of the study period, were 191 (95% CI, 145–277) and 489 (95% CI, 343–852).

**CONCLUSION:** Flexible sigmoidoscopy is a safe and practical test, and, when offered only once between ages 55 and 64 years, it confers a substantial and long-lasting benefit.

**COMMENTARY:** The UK Flexible sigmoidoscopy trial investigators led by Wendy Atkins conducted a large multicenter, randomized controlled trial that tested the impact of a single flexible sigmoidoscopy screening in a population between the ages of 55 and 64 years, who had previously indicated a willingness to undergo sigmoidoscopy on colorectal cancer incidence and mortality.<sup>2</sup> One hundred seventy thousand four hundred thirty-two eligible men and women, in 14 centers in England, Wales,

and Scotland, were randomly allocated to the intervention group (who were offered flexible sigmoidoscopy screening) or the control group (who were not contacted). The primary outcomes were the incidence of colorectal cancer and mortality from colorectal cancer. Of 375,744 men and women aged 55 to 64 years in 506 general practices who were reviewed, 368,142 were sent questionnaires regarding interest in screening. Of 194,726 who responded with interest in screening, 170,432 were randomly assigned on a 2:1 basis between controls and studied subjects. One hundred thirteen thousand one hundred ninety-five were allocated to the control group, and 57,237 were allocated to the intervention group, of whom 40,674 (71%) had a flexible sigmoidoscopy. During flexible sigmoidoscopy, small polyps were removed, and patients with large (>1 cm) polyps, villous or tubulovillous adenomas, 3 or more adenomas, or 20 or more hyperplastic polyps above the distal rectum were referred for colonoscopy. Individuals with no polyps or low-risk polyps were discharged. Trial participants were followed through the National Health Service Central Registry, cancer registries, Hospital Episodes Statistics, and the National Health Service Bowel Cancer Screening program databases.

This trial can be considered a landmark study that clearly and unequivocally shows that endoscopic screening reduces both the incidence and mortality from colorectal cancer, and it does so by a large margin in comparison with guaiac-based fecal occult blood test. The intention-to-treat analysis showed a 23% reduction (HR, 0.77; 95% CI, 0.70–0.84) in colorectal cancer incidence and a reduction of 31% (HR, 0.69; 95% CI, 0.59–0.82), whereas the per protocol analyses showed a reduction of incidence by 33% and of mortality by 43%. In addition, these results have been corroborated by a trial of similar design conducted in Italy<sup>3</sup> that achieved very similar outcomes with a 31% reduction in incidence and a 38% reduction in mortality from colorectal cancer (CRC). The incidence reduction of CRC in the distal colon was reported to be 50%, but this finding includes prevalent cancers for which the intervention could not have possibly played a role in prevention. If adjusted for the prevalent cancers, the incidence reduction in distal cancers is a truly noteworthy 70%.<sup>4</sup>

Methodologically, this is also a remarkable trial in that the investigators managed to randomly assign more than 170,000 eligible men and women, and they were able to follow up all but 12 (6 in each arm) of whom only 2 had undergone sigmoidoscopy. Overall, the extremely large numbers involved likely overcame the many potential limitations inherent in a large randomized design in which detailed demographics cannot be practically obtained, but in which baseline variations are expected to be controlled by the extremely large number of patients enrolled.

The results of the trial overwhelmingly seem to support the theoretical utility of flexible sigmoidoscopy as a

tool to prevent CRC and to save lives. The Atkins, UK Flexible Sigmoidoscopy Trial, especially when taken together with the other 2 published randomized controlled trials, provides strong evidence of a long-lasting reduction in both mortality and incidence from CRC following once-only flexible sigmoidoscopy.<sup>3,5</sup> These are truly remarkable findings and numbers that portend the potential for endoscopic screening to have a dramatic impact far above what has been achieved by guaiac-based fecal occult blood test. However, no individual modality can be interpreted in isolation.

Colorectal cancer screening may best be implemented as part of an organized, population-based screening program. Offering flexible sigmoidoscopy as a screening option in Canada would be challenging, but the strength of the evidence and the degree of the benefit requires that programs at least consider its implementation.<sup>6</sup> The most controversial issue of this topic concerns the limitations of sigmoidoscopy in examining the entire colon. This study found no effect of screening on the incidence of cancer of the proximal colon. Although this is perhaps not unexpected, several studies have shown that the risk of proximal cancers can be predicted from the characteristics of adenomas of the sigmoid and rectum.<sup>7,8</sup> This rationale was used, in this study, as a basis for referring patients for baseline colonoscopy, and this included 5% of the patients, a very conservative rate of complete colonoscopy. Therefore, the critical question is whether the results of this trial can be extrapolated to the whole colon. Although there are certainly biological and epidemiological differences between the proximal and distal colons, it would seem implausible to assume an abrupt reduction in effectiveness of endoscopic screening beyond 60 cm. Sixty centimeters was chosen as the length for a flexible sigmoidoscope for reasons of comfort and the effectiveness of a cleansing enema, not on the basis of differing pathways for the genesis of cancer. Molecular studies suggest that the changes that occur throughout the colon occur on a continuum rather than on a dichotomous basis.<sup>9</sup> There are certainly observational data that suggest that proximal endoscopic screening will not be as effective as the dramatic 70% reduction in incidence seen in the distal colon, but it is absurd to think that colonoscopy will only be effective in the proximal colon when it is done on the basis of confirming a positive stool test.

Finally, this trial did not directly address either economic issues or the feasibility of introducing such a program in North America. Practically speaking, this trial was conceived in the 1980s, conducted in the 1990s, and reported in 2010, a time frame in which both sigmoidoscopes and sigmoidoscopists have been largely supplanted by colonoscopes and colonoscopists in North America. Interpreted within this framework, pragmatists may use this trial to justify the legitimacy of colonoscopic screening and enable its widespread adoption into population-

based screening programs, whereas purists will await further results of other ongoing trials. Nonetheless, the trial was well conducted and adds strong evidence to justify endoluminal surveillance of at-risk populations with practical details worked out according to local resources and consensus. All disciplines that care for patients with diseases of the colon and rectum need to remain well trained and active in luminal endoscopy and endoscopic polypectomy.<sup>10</sup>

## ACKNOWLEDGMENT

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