

Colon Cancer Screening

The Good, the Bad, and the Ugly

THIS YEAR, IT IS ESTIMATED THAT THERE WILL be 55 170 colorectal cancer (CRC)-related deaths, making it the second leading cause of cancer-related deaths among Americans.¹ If detected early, CRC is eminently curable; however, given the insidious nature of CRC, only about one third of patients are diagnosed as having the cancer at the localized stage.¹ This underscores the need for effective screening of the population at risk, primarily those older than 50 years. There are several recommended CRC screening tests, including fecal occult blood tests (FOBTs), flexible sigmoidoscopy, and air-contrast barium enema, spanning a range of cost, invasiveness, discomfort, and accuracy.² Fecal occult blood testing is the least expensive intrusive test, whereas colonoscopy is the most accurate but also the most invasive test. Fecal occult blood testing and colonoscopy have been proved to not only decrease mortality but also prevent CRC occurrence (by 20% and 65%-90%, respectively) through identification and removal of the precursor lesion, the adenomatous polyp.^{2,3} However, CRC screening rates are significantly below those seen for breast or prostate cancer,⁴ with only one fourth to one third of eligible patients receiving any type of CRC screening.⁵

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There has been some encouraging news from comparisons between the 2002 and 2004 Behavioral Risk Factor Surveillance System surveys that demonstrated a 10% increase in the use of endoscopy for CRC screening.⁶ This may be attributable to Medicare coverage for screening colonoscopies and high-profile endorsements (eg, “the Katie Couric effect”). The increased success of these public awareness campaigns has raised an important issue—the insufficient health care resources to meet the needs. For instance, if colonoscopies were actually performed on the entire population of more than 70 million Americans older than 50 years, the annual costs would exceed \$10 billion.⁷ Moreover, many estimates suggest that entire population screening would exceed existing endoscopic capacity.⁸ Even this bleak forecast assumes appropriate use of colonoscopy (average risk screening every 10 years and postpolypectomy screening every 5 years).² However, most endoscopists perform colonoscopies more frequently than recommended, which threatens to overwhelm health care maintenance resources.⁹ The reticence of most endoscopists to abide by the extended surveillance intervals may be related to the miss rate (in expert

hands, >25% for adenomas)¹⁰ because failure to detect CRC is one of the most common causes of litigation against gastroenterologists. Further complicating limited screening capacity is that only a few colonoscopies are performed for average-risk screening, whereas there are many procedures squandered on less productive indications (eg, evaluation of irritable bowel syndrome-like symptoms).¹¹ Thus, it seems increasingly unlikely that our health care system can afford to provide access to colonoscopy for all.

In this issue of the ARCHIVES, El-Serag and colleagues¹² provide a sobering look at the state of CRC screening at the Veteran’s Administration (VA). In the VA, FOBT is not only the predominant screening test, it is actually increasing in proportion. This is in sharp contrast to the US population in general, in which FOBT use decreased from 2002 to 2004 with a corresponding increase in endoscopy.⁶ The researchers suggest that this may not necessarily lead to worse outcomes for CRC. However, several lines of evidence unequivocally indicate that FOBT is an inferior test than colonoscopy. For instance, a recent screening report¹³ showed that FOBT sensitivity for advanced neoplasia (advanced adenomas or carcinomas) was only 10.8%. In addition, one FOBT (Hemoccult II; SmithKline Diagnostics, San Jose, Calif) has been demonstrated to have only a 37% sensitivity for carcinomas.¹⁴ Furthermore, FOBT performance is worse in general practice than in clinical trials.¹⁵ Therefore, it is likely that CRC screening with FOBT will result in poorer clinical outcomes for veterans.

The reasons for the acceptance of FOBT by veterans are unclear, especially given their increased risk of colonic neoplasia.¹⁶ One potential factor is health care literacy, because it is estimated that 36% of veterans scored below the eighth-grade level and this was associated with less interest in CRC screening.¹⁷ Moreover, lower socioeconomic status (often seen in VA patients) has been independently associated with a poorer CRC screening rate.¹⁸ Thus, the VA population may be considered particularly vulnerable. While not addressed in the article, it seems logical to believe resource constraints on the VA are the driving force in the continued preference for FOBT over colonoscopy for CRC screening.

Thus, the crux of the issue is how to most efficiently use the finite endoscopic capacity. For the general population, the lifetime risk of developing CRC is approximately 6%. Performing colonoscopy on the entire population to reach a relatively small subgroup of patients who will develop colonic neoplasia is an inelegant solution. If the two thirds of the veterans who are neoplasia free

could be identified a priori and excluded from colonoscopic screening,¹⁹ this could potentially focus the limited endoscopic capacity for more effective CRC prevention efforts. Thus, targeting colonoscopy to those who are most likely to harbor colonic neoplasia is of paramount importance.

Some efforts have been made to improve fecal analysis for risk assessment. While immunohistochemical detection of hemoglobin represents an improvement, it still seems suboptimal (27.1% for advanced neoplasia).²⁰ Fecal DNA analysis has marginally improved sensitivity (18.2% for advanced adenomas), but the marked increase in costs may negate its value.¹³ Newer-generation tests with DNA methylation markers could potentially improve performance; however, clinical data are still pending.²¹

Radiology offers another approach, with air-contrast barium enema being a recommended screening test, although computed tomographic (CT) colonography seems to be superior.²² The exact sensitivities of CT colonography for advanced neoplasia are unclear, with single-center and multicenter estimates vastly differing (>90% vs 55%).²³ Preliminary studies²⁴ with newer reconstruction techniques have been encouraging, although multicenter validation studies are still pending (the ACIN 6664 trial). However, given the need for bowel cleansing and colonic air insufflation, there was no clear advantage in patient preference between CT colonography and colonoscopy.²⁴ Moreover, because 20% to 30% of patients have adenomas, performing colonoscopy for polypectomy on all patients harboring adenomas would render CT colonography non-cost-effective.²³ On the other hand, leaving small adenomas in situ may not be acceptable for physicians or patients given the premalignant nature and the occurrence, albeit uncommon, of invasive malignancy (especially in flat and depressed lesions). Because CT colonography is expensive, it may be unable to provide high-quality CRC screening in a resource-constrained society.

Several lines of evidence suggest that the “field effect” concept may allow accurate risk stratification. This is the notion that the genetic/environmental milieu that results in a lesion at one area of the colon should be detectable, at least in some form, throughout the colon. Thus, examining the distal portion of the colon (or even the rectum) should be able to predict proximal neoplasia. A common example is the use of adenomas on flexible sigmoidoscopy to determine the need for total colonoscopy (2.4-fold increased risk of proximal neoplasia).²⁵ However, sentinel distal lesions identify less than half the proximal neoplasia and are particularly poor in women.²⁶ Looking at earlier markers of the field effect, such as rectal aberrant crypt foci (via magnification chromoendoscopy), or cellular markers, such as apoptosis, is promising, but it is difficult to envision use in clinical practice.²¹ In this regard, researchers²⁷ have been interested in developing a novel biomedical optics approach that can accurately detect the nanoscale architectural manifestations of the field effect. Initial reports^{21,27} suggest that light-scattering signatures are an exquisitely sensitive and quantitative means of assessing the fundamental microarchitectural structure of the cell. Results in

experimental models have shown remarkable accuracy, and the promise of this approach has been supported by preliminary clinical studies.²⁸ If confirmed in ongoing large-scale clinical trials, the long-term goal would be to provide accurate risk assessment through a simple rectal examination using a freestanding optical probe.

In summary, finding a sensitive, well-accepted, pre-colonoscopy screening test is of paramount importance for population screening. This would ensure that colonoscopy would be used largely in patients with neoplasia, thereby sparing those patients who are unlikely to benefit from the cost, inconvenience, and potential complications. These low-risk patients may be reasonable candidates for the less invasive and less accurate tests. While there are several promising risk stratification techniques being developed, it remains to be seen whether they will be cost-effective and patient friendly enough for population screening.

In the interim, we need to encourage more of our patients to be screened. Colonoscopy is clearly the best test, but to make it more widely available, we need to be prudent about repeating studies given the low yield and long-term (10-20 years) lower risk designation achievable with a single negative colonoscopy result.²⁹ For increased intervals to be more acceptable, endoscopic miss rates need to be mitigated through rigorous assessment of quality variables, including cecal intubation rate and endoscope withdrawal time. The latter may be only possible if the draconian cuts in reimbursement rates finally cease (thereby decreasing the need for endoscopists to perform more procedures in the same allotted time). There is still a role for the less invasive and less accurate tests, especially in lower-risk patients or in those unwilling or unable to undergo more definitive screening. Until better risk stratification tools become available, tailoring screening through analysis of risk (genetic and environmental) may remain more an art than a science.

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