Colon Cancer Screening in 2005: Status and Challenges

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The field of colon cancer screening has evolved dramatically in the last 15 years regarding evidence, guidelines, and practice. In 1990, no evidence from a randomized controlled clinical trial (RCT) existed to show that colorectal cancer (CRC) screening was effective in reducing CRC mortality. In 1990, although some guidelines endorsed screening, there was disagreement among recommending organizations about which tests to recommend or whether to recommend any screening tests at all. The US Preventive Services Task Force (USPSTF), arguably the most influential of the recommending organizations and the most rigorously evidence based, said that evidence was insufficient to recommend either for or against CRC screening.[1] In this environment, CRC screening was not widely practiced, much less reimbursed by payers. If screening was performed at all, fecal occult blood testing (FOBT) was the most common test. Sigmoidoscopy was performed less frequently, and colonoscopy, rarely performed for screening, was used mainly for workup of a positive FOBT or sigmoidoscopy and for postpolypectomy surveillance. The primary questions facing academics, recommending organizations, and practicing clinicians in 1990 were (1) does CRC screening—of any kind—work to reduce CRC mortality, and (2) should it be implemented and reimbursed?

In 2005, the situation is dramatically different. We now know that CRC screening works, and it is now being implemented and reimbursed. Colonoscopy has become popular as a primary screening test, and new tests, such as virtual colonoscopy, are being developed. The purpose of this article is to identify current challenges in light of the evolution of evidence, guidelines, and practice and to anticipate the next phase of development and implementation.

Screening Average-Risk Persons: 1990–2005

1990–2000: Evidence and Guidelines Evolve to Support Colorectal Cancer Screening

In 1990, no strong evidence existed from an RCT showing that screening reduces CRC mortality. Some recommending organizations had supported it, but screening was not reimbursed or widely practiced. However, after 3 RCTs in the mid 1990s provided evidence of efficacy, a broad consensus developed among recommending organizations about performing screening and about which testing programs to recommend.[2–4] Particularly important were the USPSTF's decision in 1996 to endorse screening[2] and Medicare's decision in 2001 to reimburse for it.

Evidence about sigmoidoscopy. The first strong evidence that screening reduces CRC mortality came not from an RCT but from an unusually well done case-control study about sigmoidoscopy. Published in the *New England Journal of Medicine* in 1992, this study showed that CRC mortality was reduced by approximately 60% for lesions within reach of the instrument among persons who had had screening sigmoidoscopy.[5] Although case-control studies are generally regarded as providing weak evidence about efficacy because bias is so hard to account for compared with RCTs, this study used an unusual kind of "control group"[6] that, along with results from another study,[7] provided the rationale for the USPSTF to modify its recommendations in 1996 to include sigmoidoscopy.[2]

Evidence about fecal occult blood testing. In 1993 and 1996, 3 landmark RCTs provided evidence that FOBT screening reduces CRC mortality. Mortality reduction was 33% among subjects who had every-year rehydrated FOBT in the US trial[8] and was approximately 15% in 2 European studies for every-other-year nonrehydrated FOBT.[9,10]

Evidence about colonoscopy. Although by 1996 no study had assessed the efficacy of colonoscopy screening in reducing CRC mortality (and none has now), support for colonoscopy evolved on the basis of evidence from studies about FOBT and sigmoidoscopy. One line of reasoning is that, because colonoscopy is the means by

Abbreviations used in this paper: CRC, colorectal cancer; FOBT, fecal occult blood testing; NPS, National Polyp Study; PSA, prostate-specific antigen; RCT, randomized controlled clinical trial; USPSTF, US Preventive Services Task Force.

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which FOBT or sigmoidoscopy screening reduces mortality (because colonoscopy is performed to work up a positive primary screening test), then colonoscopy is the mechanism by which CRC mortality is reduced and should plausibly be effective as a primary screening test. A second line of reasoning is that if endoscopic screening works in the sigmoid colon, it should also work for the rest of the colon; this argument might be incorrect if the right colon behaves differently, biologically, compared with the left. Overall these arguments have been taken to indicate that colonoscopy works. Further consideration must be given to how well it works in comparison to other tests and programs, as will be discussed below.

Guidelines. Guidelines followed evidence. In 1990, some guidelines had recommended screening, although, as noted, the USPSTF did not. In 1992, the US Congress decided not to reimburse for CRC screening for Medicare patients, declining to follow recommendations based on the cost-effectiveness analysis that Congress had commissioned from the Office of Technology Assessment.[11,12] That analysis concluded, on the basis of available evidence before RCTs, that CRC screening was cost-effective compared with other medical and screening practices. However, lacking both RCT evidence and popular support for what would be a costly (even if cost-effective) program, Congress declined to support screening. By 1996, however, evidence from 3 RCTs and the case-control study dramatically changed guidelines when the USPSTF decided to endorse CRC screening.[2] That evolution of evidence and recommendations set the stage for the events of the year 2000, when CRC screening became popular.

2000: Colorectal Cancer Screening Becomes Popular and Reimbursed

By 2000, evidence about efficacy was already several years old, as was the 1996 USPSTF endorsement. However, screening was not widely practiced, and—importantly—Medicare had not decided to fully reimburse it. The events of 2000 changed the situation and provided lessons about how public policy gets made.

March 2000 became the nation's first colon cancer awareness month when Katie Couric, host of NBC's *Today Show,* promoted CRC screening after her husband's death from CRC. Couric was featured in a cover story in *Time Magazine* and produced a 5-part series on the *Today Show,* including a broadcast of her own screening colonoscopy. These events affected practice in the United States.[13,14]

In July 2000, two reports in the *New England Journal of Medicine*—and their interpretation in an accompanying editorial and the media—dramatically affected the popularity and practice of CRC screening, particularly colonoscopy. The studies were the first reports of the yield of screening colonoscopy in an asymptomatic average-risk population. Before this time, information about the prevalence of colonic neoplasms (ie, cancer and adenomas) had come from autopsy studies. Although knowing the prevalence, or yield, of screening for such lesions is related only indirectly to the outcome of CRC mortality reduction, such lesions may be considered strong surrogate outcomes because of other evidence about CRC, for example, from the RCTs of FOBT. One goal of the studies was to compare sigmoidoscopy with colonoscopy by assessing how many lesions would be missed by sigmoidoscopy. Because the expected prevalence of CRC, the most important outcome, would be too low to provide a useful comparison even in groups involving several thousand subjects, the studies also assessed (as had some previous studies) a lesion that would be more common: advanced adenomas,[15,16] generally defined as a tubular adenoma $\geq$1 cm, with villous histology, or with advanced histology. They were included as outcomes not because their natural history is known to be ominous (ie, how often and how rapidly they become incurable cancer); their natural history is unknown. Rather, they were included as possibly useful surrogates that would provide a bigger sample size for research studies to measure. Advanced adenomas have taken on a kind of life of their own in terms of becoming important targets for CRC screening.[17]

The studies found, as was widely expected, that sigmoidoscopy, which examines approximately half of the colon, misses roughly half of the lesions in the colon.[15,16] Sigmoidoscopy detects a few right-sided lesions indirectly when it discovers a lesion in the left colon considered to be a sentinel lesion that provokes a full colonoscopy. The number of right-sided lesions detected in this manner depends on what is considered a sentinel lesion, whether it is a large or advanced adenoma, an adenoma of any size, or a hyperplastic polyp. Because small adenomas and hyperplastic polyps are so common,[18,19] the decision about what is a sentinel lesion has substantial implications for workup at sigmoidoscopy screening. The 2 *New England Journal of Medicine* studies found that many right-sided CRCs and advanced adenomas were not accompanied by sentinel lesions and would be missed by sigmoidoscopy.[15,16]

This finding was not a surprise to clinicians or policy makers in the field. Sigmoidoscopy had been recommended by the USPSTF in 1996 and by other recommending organizations despite this deficiency, and it was to be recommended again in 2002, after these articles. However, in 2000, the finding was considered important