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Commentary: Choosing how to screen for colorectal cancer

The article by Choi et al in this issue of *Seminars in Oncology* [1] is an excellent review of the different modalities available for colorectal cancer screening. While one often hears that the best screening test is the one that the patient will accept (and there is truth to this axiom), for the most part one can infer from the paper by Choi et al that barium enemas and computed tomography (CT) colonography are, respectively, no longer appropriate and not yet appropriate for this purpose.

In essence, then, that leaves us with consideration of testing for fecal occult blood (either with guaiac-based testing or immunochemical testing) or endoscopic screening with either sigmoidoscopy or colonoscopy. How do we choose among them or make reasonable decisions?

Stool testing has a long history, dating back to the middle of the twentieth century. Its major drawback then was follow-up diagnostic testing; there was limited endoscopy and hence follow-up of a positive fecal occult blood test depended on a barium enema test. However, that could only indicate whether a polyp or tumor was present, but not whether it was benign or malignant. Therefore, there arose a large literature focused on the radiographic characteristics of neoplasms observed on barium enema, and how size of the neoplasm correlated with risk of a malignancy [2,3]. Above a certain size, especially if the polyp were sessile, the risk would rise to a high enough level to merit an exploratory laparotomy and partial resection. In the case of the rectum, this issue was obviated as a rigid sigmoidoscope could directly inspect the mucosal surface and biopsy or remove a polyp.

This problem was ameliorated with the invention of fiberoptics and fiberoptic endoscopy, which permitted both flexible sigmoidoscopy and colonoscopy starting in the late 1960s [4]. Thus, a positive fecal occult blood test (FOBT) could now be followed by a less invasive colonoscopy rather than surgery. This also provided the ability to remove benign adenomas, even small ones (most of which would never undergo malignant transformation), with relative ease. In most studies, FOBT leads to a positive test in 1%–3% of tests in asymptomatic average-risk adults.[5] If the test is conducted annually for screening purposes, in 10 years there will be a positive test in close to 40% [5,6]. Whether the positive test is truly linked to a bleeding neoplasm in most circumstances is moot; a positive test leads to a diagnostic colonoscopy during which one can discover an adenoma that can be removed and a future malignancy averted. In essence, one way to look at screening with annual FOBT is that it selects 40% of the population to undergo colonoscopy. The end result is that there is a 20%–30% reduction in colorectal cancer mortality with this test utilized for screening.

The point of this discussion is to indicate that, even with FOBT screening, the truth may well be that the "real," or the effector arm of screening, was performed with colonoscopy. The FOBT only served to select 40% of the screened population for colonoscopy rather than the entire population. This scenario would encourage those (likely the majority of gastroenterologists in the United States) who believe that colonoscopy is the best test for screening.

So now let us consider how it compares to its endoscopic rival, sigmoidoscopy, which has four randomized trials which showed a reduction in mortality with its use for screening [7–10]. In particular, the reduction in mortality for left-sided tumors, the region of the colorectum that the sigmoidoscope covers, can be quite dramatic, in the 60%–80% range, which translates into reductions in overall colorectal cancer mortality rates on the order of 40%.

In 1988, we published a review of sigmoidoscopy screening, at the time consisting primarily of rigid sigmoidoscopy, that concluded that sigmoidoscopic screening was probably effective in reducing colorectal cancer mortality in the region of the colorectum that it could reach [11]. With further thought, we came to a conclusion later reached by others, ie, that sigmoidoscopy was missing most of the colon, and if it was effective for the distal portion, then colonoscopy could be a better screening tool as it would also screen and treat the proximal colon. This led to our suggestion that screening colonoscopy for those at average risk for colon cancer could be a reasonable prevention measure, but that studies were needed to establish its efficacy and parameters [12].

Throughout the 1990s, colonoscopy became increasingly used for screening although not yet approved by insurance companies; presumably alternative indications were reported in order to obtain reimbursement. In 2001, Medicare officially approved screening colonoscopy for reimbursement and the test became very widely used; rates of colonoscopy underwent an even greater and sustained rise after Katie Couric underwent colonoscopy on national television [13], eventually reaching utilization rates as high as 70% in some populations over age 50 [14].

Despite this, the caveat of our original paper [12], that more studies needed to be conducted to establish its efficacy, were largely ignored. Studies were done which showed that colonoscopy could detect increased numbers of adenomas and right-sided adenomas, but no studies investigated its impact on mortality, the key variable for assessing the efficacy and utility of a cancer screening test. This changed in 2009, when a Canadian case-control study looked at the impact of colonoscopy on colorectal cancer mortality [15]. Shockingly, it found that colonoscopy had the same effect as sigmoidoscopy; it reduced mortality for

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distal colorectal cancer but not for proximal cancers. Several other studies followed that echoed these results [16], with no apparent benefit for mortality coming from colonoscopy over and above that of sigmoidoscopy. Finally, one cohort study [17] and one case-control study [18], both conducted in the United States, showed superior overall colorectal cancer mortality reduction with colonoscopy than with sigmoidoscopy, albeit the marginal gain from screening of the proximal colon was not as dramatic as the benefit for the distal colon, approximating 20%.

Thus, one is left with the fact that screening colonoscopy is the standard screening test in the United States, constituting the main test recommended by gastroenterologists. Indeed, it is almost impossible to obtain a screening sigmoidoscopy from most gastroenterologists in the United States despite the fact that it is on the list of recommended screening procedures, largely because its price is lower than that of colonoscopy, and its perceived efficacy is lower. The accompanying paper by Choi[1] compares the two tests and points out that sigmoidoscopy is less expensive (about $169 for a sigmoidoscopy *v* $600 for a colonoscopy), less invasive and dangerous, requires much less or minimal preparation, usually requires no anesthesia, does not require 24–48 hours of dietary restrictions, and can often be done by primary care practitioners or nurses.

Whether the putative gain in mortality estimated to result from colonoscopy as opposed to sigmoidoscopy is truly worth this collection of disadvantages is one that now, almost 30 years after our first commentary on the subject, we would still have to say requires more study. Unfortunately, none of the four randomized trials for colonoscopy screening compares colonoscopy to sigmoidoscopy, the most relevant comparison.

Alfred I. Neugut
Benjamin Lebwohl
Department of Medicine and
Herbert Irving Comprehensive Cancer Center,
College of Physicians and Surgeons, and
Department of Epidemiology,
Mailman School of Public Health,
Columbia University, New York NY
E-mail address: ain1@columbia.edu (A.I. Neugut)

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