Cancer Prevention Research

Perspective

Perspective on Cai et al., p. 1572, and Khalid-de Bakker, p. 1563

Examining Stools for Colon Cancer Prevention: What Are We Really Looking for?

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Abstract

Fecal immunochemical testing (FIT) is superior to guiac-based testing if we are looking for blood in stools, as it has better one-time colorectal cancer sensitivity and specificity and better patient acceptance. In this issue of the journal, Cai and colleagues (beginning on page 1572) and Khalid-de Bakker and colleagues (beginning on page 1563) present new information about the one-time test performance of FIT. FIT will have a growing appeal to providers and health care systems as resources for clinical preventive services shrink and as incentives to expand colorectal screening rates increase, but there are good reasons to be cautious about the temptation to organize new FIT screening programs. Colorectal screening has two potential objectives: To find cancers in an earlier, more-treatable stage and to find and remove adenomas to prevent cancers from forming in the first place. Because most adenomas, even advanced adenomas, do not bleed, tests designed to identify occult blood in the stool are better for detecting colorectal cancer, whereas direct endoscopic visualization of the colorectum is better for prevention. Even if advanced adenomas did commonly bleed, low compliance with repeat annual testing will seriously erode the benefit of FIT. *Cancer Prev Res; 4(10); 1531–3. ©2011 AACR.*

There is a growing body of evidence on the one-time test performance of various methods to find occult blood in stools, including two new articles in this issue of the journal reporting on the test performance of fecal immunochemical testing (FIT; refs. 1–3). Cai and colleagues show how an organized program of FIT screening in China could be complemented by a risk-factor questionnaire to achieve respectable population screening coverage with a one-time test (2). Khalid-de Bakker and colleagues remind us, however, that FIT testing has a substantially lower sensitivity for advanced adenomas than does direct endoscopic visualization (3). If occult blood in the stool is what we are looking for, then FIT is a good way to look. FIT has higher one-time sensitivity and specificity and better patient acceptance than guiac-based fecal occult blood testing (FOBT). As we interpret the findings from FIT studies such as these, however, it is important to remember what we are *really* looking for.

If we are looking for a short-term boost in screening rates for a population or higher scores on the Healthcare Effectiveness Data and Information Set (HEDIS) for our clinical organization, then FIT testing is a seductive option. However, if we are looking to prevent suffering from colorectal cancer, then endoscopic screening seems like a much better choice. The FOBT trials provided a strong proof of principle of the value of screening for reducing suffering from colorectal cancer (4–6). It is important to be clear, though, about how these FOBT screening benefits were realized. Over the decade of the Minnesota trial of annual FOBT, about a third of the screened group received a colonoscopy as a result of a positive FOBT (4). The result of these colonoscopies was a 33% reduction in colorectal cancer mortality and a 17% reduction in colorectal cancer incidence (4, 7). It is important to remember an obvious fact: There is nothing about wiping a stool sample on a card that prevented any of those cancers apart from the colonoscopy that was thus triggered when the test was positive. Screening stools for occult blood (whether by FIT or guiac-based FOBT methods) can prevent colorectal cancer only by its leading to colonoscopic examinations. The report by Khalid-de Bakker and colleagues in this issue (3) reminds us of just how poorly FIT testing performs as a first-stage screener for even advanced adenomas (15.8% sensitivity).

The fact that FIT is cheaper in the short term could reasonably sway decisions toward its use. Cost is a particularly persuasive consideration when resources are scarce. In choosing a screening method, however, it is important that we have a realistic estimate of its true effectiveness over time, not only estimates derived from combining measures of one-time testing performance with assumptions of compliance rate seen in clinical trials. Testing for occult blood in the stool needs to be done annually over a decade to approximate the 33% mortality benefit seen in the Minnesota FOBT trial. Screening less frequently will erode that benefit, a reality documented by the observation of only a

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21% mortality benefit for the group offered biannual FOBT screening in the Minnesota trial (8).

What sort of decade-long compliance might we expect with annual FIT testing? The best evidence to date indicates that a high rate of adherence to annual screening over a decade is unlikely. In a large pilot study of biannual FOBT testing in England, 58.5% of the population returned stool samples at the beginning of the screening program, and 2 years later, at the time of the second round of screening, that proportion was 51.9% (9). Overall, only about 48% of people returned samples at both the initial round of testing and 2 years later. This is a disappointingly low proportion for only the first 2 years of a new program of long-term biannual screening. Furthermore, about 20% of those testing positive in each of the first 2 rounds of screening failed to follow through with a colonoscopy. As return rates for subsequent rounds are not likely to be substantially higher than the rates observed at the beginning of this program, it is probable that only a third of the population will be effectively screened. Therefore, the hoped-for 17% to 21% mortality reduction from biannual FOBT screening in England may actually be within the range of 5% to 10%. The pilot FIT screening program in China reported by Cai and colleagues produced return rates of 76.4% at the time of the invitation for the first screening, which is a very high rate (2). However, only 78.7% of those who tested positive went on to receive colonoscopy, thus reducing the effective screening coverage to 60% for the initial round of screening. Even in China, where compliance in public health programs is often remarkably good, more than 50% adherence to decade-long serial FIT screening may not he achievable.

Therefore, if using FIT to look for blood in the stool once a year could reduce colorectal cancer mortality by 33% but adherence issues limit this benefit to closer to a 10% to 15% mortality reduction, is FIT still a good option? Yes, any mortality reduction is better than none, but if we are choosing FIT based on a belief that it is more cost-effective, we need to be clear on whether that belief is true. Endoscopy is much more effective for colorectal cancer prevention than is any method based on looking for blood in the stool. One-time sigmoidoscopy reduced the incidence of cancers within the scope-visible part of the colorectum by 50% over a decade in a randomized trial, and various observational studies of sigmoidoscopy and colonoscopy estimate colorectal cancer risk reductions in the range of 60% to 80% (10–13). Of course, endoscopic screening is also not effective if it does not get done, but a lot of endoscopic screening is getting done. In 1999, 43.9% of U.S. adults older than 50 years reported ever having a lower gastrointestinal endoscopy; by 2010, this figure increased to 65.2% (14). Against this background, organized FIT testing programs in the United States are best framed as programs that provide an alternative to direct endoscopic screening in an overall blended program that rigorously advances all screening options (15).

The cost of colorectal screening is an important consideration. A detailed discussion of comparative cost-effectiveness is beyond the scope of this article, but several analyses indicate very favorable cost–benefit ratios for endoscopic screening approaches, with some estimates even showing a cost saving of endoscopic screening in the long term (16). In considering the costs of a FIT program compared with those of a colonoscopy program, it is important to remember that FIT screening must be repeated each year for a decade, whereas colonoscopy is a once-per-decade test for most people. Surprisingly, the decade-long costs of a FIT program (the annual FIT costs plus the costs of colonoscopy in the approximately 5% of people with a positive FIT each year) end up being similar to the costs of an endoscopic screening program. In recent years in Colorado, we have operated a colonoscopic screening program for the medically underserved, funded by a state tobacco tax. The total direct cost of a colonoscopy in our program, including all the fees for the provider, facility costs, the anesthesia, and any needed pathology, is about $900 per person screened. The direct cost of a decade of annual FIT testing would be about $240 (10 annual tests of $24 each), but adding in the colonoscopy costs for the approximately 40% of screenees who would be expected to need a colonoscopy after a positive FIT within the decade increases the estimated total direct cost per person to about $600. In addition to these direct costs for testing, the program management costs of a decade-long effort of tracking and prodding for compliance would be greater for a FIT program.

The total program costs of annual FIT over a decade are thus surprisingly similar to those of colonoscopy, but with quite different expected benefits. Formal cost–benefit comparisons of colon endoscopy versus FOBT strategies indicate very similar cost–benefit ratios, but because of the accelerating costs of treatment for colorectal cancer in recent years, the cost–benefit ratio of endoscopic screening is now becoming more favorable (16). Nonetheless, short-sightedness brought on by the economic reality of the moment can often trump long-term planning. Because the recent economic recession has led to a substantial reduction of funding to the Colorado Colorectal Screening Program, even in Colorado we are now turning more to FIT as a short-term solution for colorectal screening.

Colorectal screening technology continues to advance. Abdominal imaging technology is improving (17), and important progress is also being made in both stool-based and circulation-based molecular assays (18, 19), which may be quite specific for advanced colorectal neoplasia. Although we do not seem to be on the immediate verge of useful new screening technologies, it is likely that within the coming decade, we will have much easier ways to screen for advanced colorectal neoplasia. Because our future choices are likely to be more numerous and also better than our current choices, whatever methods we now choose need not be seen as lifelong policies as much as choices that can bridge us for a decade until better methods become available.

FIT is a lot better than no testing, but we need to remember that the eventual effectiveness of FIT will be achieved in proportion to the extent that it really gets done. It is only the exceptionally well-organized health care system that can actually accomplish high rates of compliance with annual

\stool testing (15). As we make decisions about how to screen for the coming decade, we need to be honest about what degree of compliance we can expect and clear about what we are really looking for. If we are looking for a short-term method to increase metrics of screening rates or HEDIS scores, then FIT is a good choice. If we do make this choice, though, we need to be realistic about the small size of the health benefit we are really likely to see. If, however, we are looking for the best way to reduce suffering from colorectal cancer over the coming decade, then primary endoscopic screening looks like a much better choice.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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