Recent Developments in Colorectal Cancer Screening and Prevention

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Colorectal cancer is a significant contributor to morbidity and mortality in the United States. Studies published in the early 1990s, showing that screening for colorectal cancer can reduce colorectal cancer–related mortality, led many organizations to recommend screening in asymptomatic, average-risk adults older than 50 years. Since then, however, national screening rates remain low. Several important studies published over the past four years have refined our understanding of existing screening tools and explored novel means of screening and prevention. The most important new developments, which are reviewed in this article, include the following: Additional trial results support the effectiveness of fecal occult blood testing in reducing the incidence of, and mortality from, colorectal cancer. New studies document the sensitivity of fecal occult blood testing, sigmoidoscopy, and double-contrast barium enema compared with colonoscopy. Cost-effectiveness models show that screening by any of several methods is cost-effective compared to no screening. Randomized trials show that calcium is effective but fiber is not effective in preventing reoccurrence of adenomatous polyps. Preliminary data suggest that nonsteroidal anti-inflammatory drugs may prevent adenomatous polyps and that DNA stool tests and virtual colonoscopy may show promise as screening tools. This new information provides further support for efforts to increase the use of colorectal cancer screening and prevention services in adults older than 50 years. (Am Fam Physician 2002;66:297-302. Copyright© 2002 American Academy of Family Physicians.)

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The American Cancer Society estimated that more than 57,000 people would die of colorectal cancer in the United States in 2001, making this the second leading cause of cancer deaths overall.[1] In the early 1990s, two studies demonstrated that screening for colorectal cancer with fecal occult blood testing (FOBT) or sigmoidoscopy was effective in reducing disease-specific mortality.[2,3] [Reference 2—Evidence level A: randomized controlled trial (RCT); Reference 3—Evidence level B: case-control study] Since that time, most guideline-issuing organizations have recommended colorectal cancer screening for asymptomatic adults older than 50. Screening rates, however, remain low. Recent data from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System (BRFSS), a telephone-based survey of U.S. residents, show that only 44 percent of adults older than 50 report having been screened with either FOBT within the past year or flexible sigmoidoscopy or colonoscopy within the past five years.[4]

See pages 185 and 200 for EBM background, and page 190 for definitions of strength-of-evidence levels.

From 1998 to 2001, eight important new research findings have expanded and refined our knowledge about screening and prevention. *Table 1*[2,5-22] summarizes these findings.

Data Sources

Candidate articles were identified through a systematic search of the literature undertaken as part of a comprehensive review of colorectal cancer screening for the U.S. Preventive Services Task Force (USPSTF). The review included a MEDLINE search of articles published from 1998 to 2001 using the terms colorectal neoplasms and mass screenings. The

review also included bibliographies of the identified articles and the recommendations of peer reviewers. (The full report of the review, including new screening recommendations from the USPSTF, is available at www.ahrq.gov/clinic/epcix.htm.)

Findings

SCREENING

• FOBT performed every two years effectively reduces colorectal cancer mortality, but less so than annual testing.

A 1993 randomized trial[2] in Minnesota of colorectal cancer screening with FOBT showed that, after 13 years of follow-up, annual screening reduced colorectal cancer mortality by 33 percent (95 percent confidence interval [CI]: 13 to 50 percent). Biennial (every two years) screening did not achieve a statistically significant reduction in colorectal cancer mortality (relative risk [RR]: 0.94; 95 percent CI: 0.68, 1.31). About 80 percent of the test slides were rehydrated (i.e., a drop of water was added to the slides before they were developed). Rehydrating increases sensitivity and decreases specificity. Among patients tested annually, 38 percent underwent a colonoscopy over the 13-year trial, compared with 28 percent of those tested biennially. [Evidence level A: RCT]

Recent evidence has emerged showing that biennial testing also reduces mortality, although less so than annual testing. Two European studies[5,6] showed that biennial FOBT reduced colorectal cancer mortality by 15 to 18 percent, using mostly nonrehydrated slides over eight or 10 years. [Reference 5—Evidence level A: RCT; Reference 6—Evidence level A: RCT] Far fewer patients (about 5 percent in each trial) underwent colonoscopy. In 1999, the Minnesota investigators presented 18-year follow-up data demonstrating that biennial testing reduced colorectal cancer mortality by 21 percent (95 percent CI: 3 to 38 percent).[7] [Evidence level A: RCT]

On the basis of data from these trials, about 1,000 people would need to be screened annually over 10 years to prevent one death from colorectal cancer.[23] [Evidence level A: meta-analysis]

• FOBT reduces the incidence of colorectal cancer.

The ability to detect precancerous adenomatous polyps, remove them, and thus prevent the development of colorectal cancer is an important rationale for screening. Some have suggested that the poor sensitivity of FOBT for detecting adenomas makes it ineffective for preventing cancer and, hence, inferior to endoscopic screening techniques.

However, recent findings from the 18-year follow-up of the Minnesota trial suggest that FOBT can reduce colorectal cancer incidence.[8] [Evidence level A: RCT] Persons randomized to FOBT (annual or biennial, 83 percent

TABLE 1
Colorectal Screening and Prevention: Evidence-Based Medicine Summary

*Level of evidence**	*Clinical implications*
A	FOBT performed every two years is effective in reducing colorectal cancer mortality but less so than annual testing.
A	FOBT reduces the incidence of colorectal cancer.
B	Barium enema sensitivity is lower than previously estimated.
B	Colonoscopy is more accurate than flexible sigmoidoscopy and FOBT for detecting colorectal neoplasia, but the implications for screening policy are unclear.
B	DNA stool test and virtual colonoscopy show early promise for detection of colorectal neoplasia, but further research is required.
A	Increased fiber intake does not prevent recurrent colorectal adenomas in middle-aged adults.
A	Calcium supplements reduce the risk of recurrent colorectal adenomas.
A	NSAIDs, including COX-2 inhibitors, reduce the risk of adenomas in patients with high-risk familial syndromes.

FOBT = fecal occult blood testing; NSAIDs = nonsteroidal anti-inflammatory drugs; COX-2 = cyclooxygenase-2.

**—Highest level of evidence presented in this review article. See page 190 for definitions of strength-of-evidence levels.*

Information from references 2, and 5 through 22.

rehydrated slides) had a reduced incidence of colorectal cancer compared with unscreened control subjects (RR reduction: 17 to 20 percent). It is unclear whether this reduction comes from direct detection of bleeding adenomas by FOBT or by chance detection of adenomas during colonoscopies performed after FOBTs that were falsely positive.[24]

• Barium enema sensitivity is lower than was previously estimated.

Double-contrast barium enema (DCBE) has been advocated as a possible screening test for colorectal cancer by several guideline-issuing organizations, despite the lack of any studies examining its effectiveness in a screening population. Previous studies of the accuracy of barium enema suggested that the sensitivity and specificity of DCBE were both in the 80 to 90 percent range,[25] and older cost-effectiveness analyses have suggested that DCBE would be cost-effective if it had these same test characteristics.[26] Unfortunately, the quality of the studies used to derive the estimates of test accuracy was poor, and none of these studies were performed in screening populations.

In a recent evaluation of the accuracy of DCBE, patients with a history of adenomas underwent DCBE and colonoscopy three and six years after initial polypectomy.[9] [Evidence level B: nonrandomized clinical trial] A total of 580 patients (74 percent men, 61 percent age 60 and older) were examined. The sensitivity of DCBE (compared to colonoscopy) for finding adenomas less than 0.5 cm in diameter was 32 percent (95 percent CI: 25 to 39 percent); for adenomas of 0.6 to 1 cm, it was 53 percent (95 percent CI: 40 to 66 percent); for adenomas larger than 1 cm, including two malignant adenomas, it was 48 percent (95 percent CI: 24 to 67 percent). No frank cancers were detected. Of 470 examinations in which no adenomas were identified on colonoscopy, barium enema was positive in 83 (specificity of 85 percent).

Although not performed in a screening population, this study suggests that DCBE may be less sensitive than was previously thought. Further study of DCBE in a true screening population is warranted to clarify this issue.

Double-contrast barium enema may be less sensitive than was previously thought.

• Colonoscopy is more accurate than flexible sigmoidoscopy and FOBT in detecting colorectal neoplasia, but the implications for screening policy are unclear.

One study examined the relative accuracy of rehydrated FOBT, flexible sigmoidoscopy, and colonoscopy in 2,885 asymptomatic adults (97 percent men), ages 50 to 75, in the Veterans Administration health care system.[10] [Evidence level B: nonrandomized clinical trial] FOBT detected 50 percent of patients with cancer and 24 percent of patients with advanced neoplasia (defined as cancers), villous adenomas, adenomas with high-grade dysplasia, or large (greater than 1 cm) tubular adenomas. Colonoscopy was performed in all study participants; examination of the rectum and sigmoid colon during colonoscopy was defined as a surrogate for sigmoidoscopy. Sigmoidoscopy alone detected 70 percent of patients with advanced neoplasia. The combination of FOBT and sigmoidoscopy detected 76 percent, which represents a small and statistically insignificant increase in rate of detection compared with the rate of sigmoidoscopy alone.

These data have been interpreted by some to mean that screening with colonoscopy is the most effective and, thus, the preferred test. However, the sensitivity levels found in this study are very similar to estimates used in several cost-effectiveness models that have not all found colonoscopy (or any other test) to be clearly the most effective or cost-effective method of screening.[11-13]

• Several methods of colorectal cancer screening are cost-effective compared with no screening, but current evidence is not sufficient to determine the most effective or cost-effective test.

Colonoscopy every 10 years or the combination of flexible sigmoidoscopy and fecal occult blood testing are the most effective strategies in terms of life-years saved.

Frazier and associates,[11] Khandker and associates,[12] and Sonnenberg and associates,[13] each examined the cost-effectiveness of several major screening strategies for colorectal cancer, including annual FOBT alone, sigmoidoscopy alone every five or 10 years, and colonoscopy alone every 10 years. Frazier and Khandker, but not Sonnenberg, examined DCBE alone every five years, as well as the combination of FOBT annually and sigmoidoscopy every five years. Each of the analyses modeled the effects of screening on a cohort of patients, with screening beginning at age 50. The model inputs were derived from the literature and required some assumptions about the biologic behavior of cancers and polyps.

All methods of screening were cost-effective compared with no screening, with cost-effectiveness ratios from approximately $10,000 to $25,000 per year of life saved. These cost-effectiveness ratios compared favorably with other commonly accepted preventive care strategies such as treatment of moderate hypertension or use of screening mammography in women older than age 50. Most studies found that either colonoscopy alone every 10 years or the combination of flexible sigmoidoscopy and FOBT were the most effective strategies in terms of life-years saved. Uncertainties about basic aspects of colorectal cancer biology—as well as variations in the ways costs, complications and especially compliance were modeled—led to differences in each study's conclusions about which strategy is most cost-effective.

• DNA stool test and virtual colonoscopy show early promise for detection of colorectal neoplasia, but further research is necessary.

Substantial research has been directed toward developing better noninvasive tests for colorectal neoplasia. One study evaluated a new stool test that attempts to detect changes in DNA associated with colorectal neoplasia.[14] Stool samples were tested from 22 patients with colorectal cancer, 11 with large adenomas, and 28 with endoscopically normal colons. Early results of the evaluation showed a sensitivity of 91 percent for cancer (95 percent CI: 71 to 99 percent) and 82 percent for adenomas (95 percent CI: 48 to 98 percent); specificity was 93 percent (76 to 99 percent).

In another study, researchers collected stool DNA and found that three genetic markers together detected 71 percent (95 percent CI: 56 to 83 percent) of 51 patients with colorectal cancer.[15]

Virtual colonoscopy, or computed tomographic colography, is another emerging technology for colorectal cancer screening. Virtual colonoscopy was performed in a study of 100 patients at high risk for colorectal cancer before conventional colonoscopy.[16] Researchers found a sensitivity of more than 90 percent for cancers and large polyps. Specificity was approximately 80 percent. [Evidence level B: nonrandomized clinical trial]

Although the early results for these new technologies are promising, further study in

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larger sample populations of average-risk screening patients is necessary before they can be widely implemented.

A high-fiber diet over one to four years is not effective in preventing new adenomas in persons with previous colorectal adenomas.

PREVENTION

• Increased fiber intake does not prevent recurrent colorectal adenomas in middle-aged adults.

Observational evidence suggests that persons who consume a high-fiber diet are less likely to develop or die from colorectal cancer. Two recent studies[17,18] examined whether increasing dietary fiber could reduce the development of colorectal adenomas in patients with previously diagnosed adenomas.

One study[17] randomized 2,079 adults who had recently had an adenoma removed to either a high-fiber, low-fat diet or their usual diet. [Evidence level A: RCT] Intervention subjects were successful in changing their diets but did not have fewer adenomas on colonoscopy at one or four years, compared with control subjects (39.7 versus 39.5 percent).

The other study[18] randomized 1,429 adults with previous adenomas to a high dose of wheat-fiber supplement (13.5 g per day) or a low dose of the supplement (2 g per day). [Evidence level A: RCT] There was not a statistically significant difference in the rate of new adenomas after three years (47 versus 51 percent, $P = 0.13$). It appears that use of a high-fiber diet over one to four years is not effective in preventing new adenomas in patients with previous colorectal adenomas. Whether high-fiber diets can prevent colorectal cancer or adenomas if implemented at an earlier age or continued for longer periods remains unknown.

• Calcium supplementation reduces the risk of recurrent colorectal adenomas.

In one study[19] of calcium supplementation, 913 patients with a previous history of colorectal adenomas were randomized to receive high-dose calcium carbonate supplements (3 g [1,200 mg] of elemental calcium per day) or placebo over four years. [Evidence level A: RCT] Analysis was restricted to the 832 patients (409 in the calcium group and 423 in the placebo group) who completed both follow-up examinations. They found a lower rate of adenoma recurrence in patients taking calcium (rate of new adenomas: 31 versus 38 percent; RR: 0.85; 95 percent CI: 0.74, 0.98). The seven percentage-point absolute difference in new adenomas over four years suggests that about 15 patients would need to take calcium for four years to prevent one new adenoma.

A recent three-year randomized trial[20] achieved a similar result in Europe. The effect of calcium supplementation in patients with no previous history of polyps has not been examined, nor has its ability to prevent cancers.

• Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, reduce the risk of adenomas in patients with high-risk familial syndromes.

Sulindac (Clinoril), an older NSAID, has been shown in randomized trials to prevent colorectal neoplasia in patients with familial polyposis,[21] although not approved for this use by the FDA. A recent randomized trial[22] found that celecoxib (Celebrex), a COX-2 specific NSAID, was also effective in this population. [Evidence level A: RCT] The effectiveness of these agents seems confined to the time the person is actually taking the drug; polyp growth recurs when it is stopped.

The effectiveness of NSAIDs, including COX-2 inhibitors, in average-risk patients has not been determined and is the subject of continuing trials.

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