Colorectal Cancer: A Summary of the Evidence for Screening and Prevention

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Colorectal cancer causes significant morbidity and mortality in the United States. The incidence of colorectal cancer can be reduced with increasing efforts directed at mass screening of average-risk adults 50 years and older. Currently, fecal occult blood test and flexible sigmoidoscopy have the highest levels of evidence to support their use for colorectal cancer screening. Colonoscopy does not have a proven colorectal cancer mortality benefit, but it does have the greatest single-test accuracy, and it is the final test in the pathway to evaluate and treat patients with other abnormal screening tests. Double-contrast barium enema has sparse data of effectiveness. Computed tomographic colonography, fecal DNA testing, and Pillcam Colon are promising tests that need further study before they can be recommended for widespread screening. Routine screening should continue until 75 years of age. There is good evidence that fiber and antioxidants are not effective for primary prevention of colorectal cancer; they should not be recommended for chemoprevention. There is good evidence that aspirin, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors are effective for decreasing the risk of colorectal cancer and adenomatous polyps, but increased risks, such as gastrointestinal bleeding, limit their usefulness. There is fair evidence that obesity is associated with colorectal cancer. Additional studies are needed on decreased fat intake and red meat consumption, and the use of calcium, vitamin D, and statins before these can be recommended for primary prevention of colorectal cancer. (*Am Fam Physician.* 2008;78(12):1385-1392, 1393-1394.

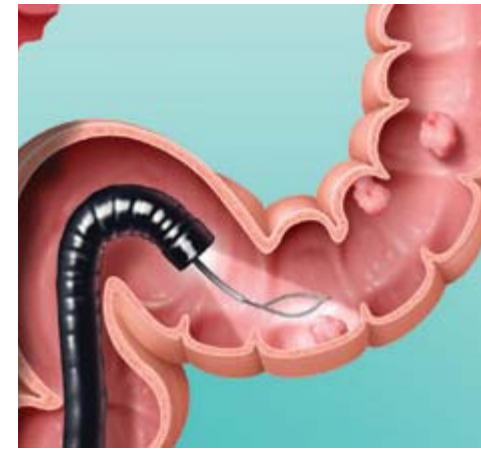

ILLUSTRATION BY JOHN W. KARAPELOU

▶ **See related editorial on page 1340.**

▶ **Patient information:** A handout on colon cancer screening, written by the authors of this article, is provided on page 1393.

Colorectal cancer is the third most common cancer in the United States and the second most common cause of cancer-related death.[1] Most colorectal cancers arise from preexisting adenomatous polyps. Adenomatous polyps occur in 30 percent of adults 50 years and older, and the incidence increases with advancing age.[2] The goal of colorectal cancer screening is to identify early cancers and adenomatous polyps by mass screening of all average-risk adults 50 years and older.[3-6] Routine screening should continue until 75 years of age.[6] The U.S. Preventive Services Task Force (USPSTF) recommends against continued routine screening in previously screened adults 76 to 85 years of age and against any screening in adults older than 85 years.[6] Adenomatous polyps can be removed during colonoscopy by polypectomy, which reduces the expected incidence of colorectal cancer.[3,7]

Colorectal Cancer Screening

An average-risk adult is defined as an asymptomatic person without a personal or family history of adenomatous polyps or other illness (e.g., inflammatory bowel disease, familial adenomatous polyposis, hereditary nonpolyposis colon cancer) that predisposes to colorectal cancer. Persons at increased risk require more intensive screening. The American Academy of Family Physicians strongly recommends that adults 50 years and older be screened for colorectal cancer.[4] This is consistent with the recommendations of other organizations *(Table 1)*.[3-6,8] Only 24.1 percent of Americans have completed a fecal occult blood test (FOBT) within the past two years, and only 57.1 percent have

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Colorectal cancer screening			
All adults 50 years and older should be screened for colorectal cancer.	A	3-6, 12	Most colorectal cancers arise from adenomatous polyps.
Routine screening for colorectal cancer should continue until 75 years of age.	A	6	The U.S. Preventive Services Task Force recommends against continued routine screening in previously screened adults 75 to 85 years of age and against any screening in adults older then 85 years.
Options for colorectal cancer screening include:			
Annual FOBT	A	12, 13	Decreased mortality from colorectal cancer, but not all-cause mortality
Flexible sigmoidoscopy every five years (with or without FOBT)	A	6, 12, 16-18, 20	Decreased mortality from colorectal cancer; effect on all-cause mortality unknown Mortality benefit less in black persons older than 60 years and in women
Colonoscopy every 10 years	B	3, 7, 12, 24, 25	Mortality benefit not proven Greater single-test accuracy than FOBT or sigmoidoscopy, but higher risk of serious complications
Primary prevention of colorectal cancer			
Fiber supplementation should not be recommended to decrease the risk of colorectal cancer.	A	49	Not recommended for chemoprevention; no evidence of benefit
Aspirin and nonsteroidal anti-inflammatory drugs should not be routinely used for chemoprevention of colorectal cancer.	A	50	Increased harms, such as gastrointestinal bleeding and renal impairment, limit routine use
Risks and benefits should be considered when recommending hormone therapy for women to decrease the risk of colorectal cancer.	B	54, 55	Good evidence of benefit to decrease the risk of colon cancer; inconsistent evidence for rectal cancer Increased risk of more advanced colon cancers with estrogen use; estrogen use associated with thromboembolic events and breast cancer
Antioxidants should not be recommended to decrease the risk of colorectal cancer.	A	57	Not recommended for chemoprevention; vitamin E associated with increased risk of adenomatous polyps

FOBT = fecal occult blood test.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

ever completed a sigmoidoscopy or colonoscopy.[9] Most organizations do not recommend a preferred screening method, but instead list screening options, including FOBT, flexible sigmoidoscopy, and colonoscopy.

Colorectal cancer screening is cost-effective (less than $30,000 per additional year of life gained), regardless of the screening method,[10] and it has been estimated that routine screening could save 18,800 lives per year.[11] There is emerging evidence on newer technologies for colorectal cancer screening, including computed tomographic colonography, fecal DNA test, and Pillcam Colon. However, it remains uncertain how these newer technologies can best be used in mass screening.

FECAL OCCULT BLOOD TEST

Early detection of occult bleeding from colorectal cancer or polyps can be done using FOBT. The FOBT should be performed using testing cards sent home with the patient. Office testing of stool samples obtained by digital rectal examination has not been shown to reduce

Table 1. Summary of Primary Colorectal Cancer Screening Recommendations in Average-Risk Persons*

Organization	*Recommendations*
American Academy of Family Physicians[4]	It is strongly recommended that adults 50 years and older be screened for colorectal cancer.
American Cancer Society[5]	Asymptomatic adults 50 years and older should be offered colorectal cancer screening options using methods that detect cancer and polyps or cancer alone.
	Options for detecting polyps and cancer include flexible sigmoidoscopy, double-contrast barium enema, or computed tomographic colonography every five years; or colonoscopy every 10 years.
	Options for detecting primarily cancer include FOBT or a fecal immunochemical test every year; or a fecal DNA test (no recommended interval).
American College of Gastroenterology[3,8]	Colonoscopy is the preferred modality for colorectal cancer screening (grade B recommendation: observational studies).
	Alternative methods for screening include FOBT every year (grade A recommendation: prospective controlled trials); flexible sigmoidoscopy every five years; and combined yearly FOBT and flexible sigmoidoscopy every five years (grade B recommendation: observational studies).
	Studies of computed tomographic colonography and fecal DNA testing for colorectal screening have yielded conflicting results; therefore, these tests cannot be recommended (grade A recommendation: prospective controlled trials).
U.S. Preventive Services Task Force[6]	It is strongly recommended that adults 50 years and older be screened for colorectal cancer (grade A recommendation).
	Routine screening should continue until 75 years of age in persons with negative previous screening (grade A recommendation).
	There is convincing evidence that screening with FOBT, flexible sigmoidoscopy, or colonoscopy reduces mortality from colorectal cancer in adults 50 to 75 years of age (grade A recommendation).
	There is insufficient evidence that newer screening modalities improve health outcomes (grade I recommendation).

FOBT = fecal occult blood test.

**—Average risk is defined as asymptomatic and without a personal or family history of adenomatous polyps or other illness (e.g., inflammatory bowel disease, familial adenomatous polyposis, hereditary nonpolyposis colon cancer) that predisposes to colorectal cancer. Persons at increased risk require more intensive screening.*

Information from references 3 through 6 and 8.

mortality. A single FOBT performed by digital rectal examination will miss 95 percent of colorectal cancers and is not recommended for screening.[12] Rather, patients should take home three cards with two testing windows on each card, and be instructed to use one card a day for three consecutive days. Rehydration of stool cards with water before development may improve sensitivity, but it also leads to increased false-positive results.[12]

A Cochrane systematic review showed a reduction in colorectal cancer mortality of 16 percent with FOBT (relative risk [RR] = 0.84; 95% confidence interval [CI], 0.78 to 0.90).[13] Overall, 10,000 persons need to complete FOBT annually to prevent 8.5 deaths from colorectal cancer over 10 years (number needed to screen = 1,176).[13] Benefits of screening with FOBT include a modest reduction in colorectal cancer mortality and a potential reduction in cancer incidence through the early identification and removal of adenomatous polyps. Reduction in colorectal cancer mortality for FOBT is based on standard guaiac-based testing (Hemoccult II). In a departure from their 2002 guidelines,[12] the USPSTF now specifically recommends annual FOBT using high-sensitivity guaiac-based testing (Hemoccult Sensa).[6] The USPSTF based their conclusions on computer simulation modeling that shows life-years gained using high-sensitivity guaiac-based testing similar to that of colonoscopy every ten years (at the expense of increased false-positive results).[14]

Fecal immunochemical testing is a newer way to detect occult blood in stool. There have been no randomized trials that show a decrease in colorectal cancer mortality with fecal immunochemical testing. Sensitivity is higher than guaiac-based testing at the cost of a slightly higher false-positive rate.[15] The American Cancer Society recommends FOBT or fecal immunochemical testing every year.[5] Unlike FOBT, fecal immunochemical testing does not require dietary restrictions before testing. A positive test should be followed up with a colonoscopy.

FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy every five years is an accepted modality for colorectal cancer screening by most recommending organizations *(Table 1)*.[3-6,8] The USPSTF now

recommends combining sigmoidoscopy every five years with high-sensitivity FOBT every three years.[6] A 1992 case-control study found a colorectal cancer mortality reduction benefit of 60 percent in persons having a polyp within the reach of the sigmoidoscope.[16] Two other case-control studies also showed a significant mortality benefit for patients 50 years and older.[17,18] This mortality benefit may be less in women, who were twice as likely to harbor neoplasia that would have gone unidentified by flexible sigmoidoscopy in a prospective screening trial.[19] Black persons older than 60 years may be more likely than white persons to have a large polyp (greater than 9 mm) beyond the reach of sigmoidoscopy, as shown by a large prevalence study of 85,525 asymptomatic persons.[20]

Colonoscopy has superior single-test accuracy compared with other screening modalities.

Compared with colonoscopy, sigmoidoscopy carries other relative benefits, particularly improved safety and lowered costs. The rate of perforation for flexible sigmoidoscopy is one in 25,000[21] to 50,000 procedures[22] compared with 5.6 per 10,000 procedures for colonoscopy (95% CI, 2.2 to 14.5 per 10,000 procedures).[23] Overall, serious complications that require hospitalization occur in 3.4 per 10,000 flexible sigmoidoscopy procedures (95% CI, 0.6 to 19 per 10,000 procedures) compared with 31 per 10,000 colonoscopy procedures (95% CI, 17 to 58 per 10,000 procedures).[23] Sigmoidoscopy is usually not performed using conscious sedation. Patients who are not sedated can provide the endoscopist with sensory feedback, theoretically limiting barotrauma and endoscopic abrasions.[22] A partial bowel preparation is necessary the evening before or the morning of the procedure.

COLONOSCOPY

Several organizations recommend colonoscopy once every 10 years for screening in average-risk persons *(Table 1)*.[3-6,8] Two nonrandomized trials have reported the benefits of screening colonoscopy in asymptomatic adults,[24,25] and there is a large body of evidence indicating that polypectomy significantly decreases the incidence of colorectal cancer.[3,7] Colonoscopy has superior single-test accuracy compared with other screening modalities, and it is the final test in the pathway to evaluate and treat patients with other abnormal screening tests. One trial reported that, compared with colonoscopy, sigmoidoscopy combined with FOBT failed to identify 24 percent of advanced colonic neoplasia.[26] A recent meta-analysis reported that colonoscopy is more accurate at detecting polyps than computed tomographic colonography or double-contrast barium enema.[27] A systematic review found a miss rate of 2.1 percent for adenomatous polyps 10 mm or larger, and a miss rate as high as 26 percent for smaller polyps.[28] In a retrospective cohort study of 1,256 persons, the incidence of advanced adenoma was 1.3 percent and no colorectal cancers were found on rescreening with colonoscopy after a mean of 5.3 years following a negative colonoscopy.[29]

Colonoscopy carries a greater risk of perforation and other serious complications than sigmoidoscopy. Most perforations with colonoscopy (65 percent) occur in the sigmoid colon.[22] Colonoscopy is routinely performed using conscious sedation, which improves comfort, but increases the risk of cardiopulmonary complications. A complete bowel preparation is necessary the day before the examination. Patients undergoing colonoscopy miss a day from work and require a chaperone for transportation following the procedure. Cost and access are significant barriers to adopting colonoscopy as a primary screening method. One study found that the median cost of colonoscopy in the United States was $1,736.[30]

DOUBLE-CONTRAST BARIUM ENEMA

Before the introduction of colonoscopy in the early 1970s, barium enema was the primary means of detecting colonic polyps. Double-contrast barium enema is still used as a screening tool, particularly for the assessment of the right side of the colon following an incomplete colonoscopy. However, the effectiveness of double-contrast barium enema has yet to be studied in a screening population. Double-contrast barium enema is safe, with a perforation rate of one in 25,000.[31]

Double-contrast barium enema has been compared directly with colonoscopy in a well-designed, blinded study of surveillance after polypectomy as part of the National Polyp Study.[32] In all, 862 paired colonoscopic and double-contrast barium enema examinations were performed. Adenomatous polyps were detected in 242 colonoscopic examinations (28 percent). Of these, double-contrast barium enema found one or more adenomatous polyps in 94 examinations (rate of detection of 39 percent; 95% CI, 33 to 45). The rate of adenomatous polyp detection for double-contrast barium enema was significantly related to the size of the polyp (32 percent for polyps 5 mm or smaller, 53 percent for those 6 to 10 mm, and 48 percent for those larger than 10 mm). The rate of detection was also significantly higher for the left side of the colon ($P = .01$). Double-contrast barium enema identified 12 additional adenomatous polyps (in 11 patients) not visible on initial colonoscopy (none

were larger than 10 mm); however, the cost-effectiveness of combining double-contrast barium enema and colonoscopy is unknown.

COMPUTED TOMOGRAPHIC COLONOGRAPHY

Computed tomographic colonography, or virtual colonoscopy, requires a complete bowel preparation, followed by air insufflation into the rectum through a rectal tube. Thin-section, helical computed tomographic images are then acquired over 10 to 15 minutes and reconstructed into virtual three-dimensional images by a computer.

Studies of computed tomographic colonography have reported sensitivities of 55 to 100 percent and specificities of 86 to 98 percent for detection of polyps larger than 10 mm compared with colonoscopy. Accuracy is substantially less for smaller polyps.[33-38] A case-control study of 6,283 persons compared computed tomographic colonography with colonoscopy for detection of "advanced neoplasia" (defined by histologic criteria or polyp size 10 mm or larger). Detection rates were similar (3.2 and 3.4 percent, respectively), but the computed tomographic colonography screening group experienced fewer polypectomies and complications.[39] In this study, the referral rate for colonoscopy in the computed tomographic colonography group was 7.9 percent. A prospective study of 2,600 asymptomatic persons showed that computed tomographic colonography detected nine out of 10 large adenomatous polyps or cancers 10 mm or larger found by colonoscopy (sensitivity of 90 percent, specificity of 86 percent). The projected colonoscopy referral rate was 17 percent.[38] In this study, 66 percent of patients had extracolonic findings found by computed tomographic colonography, and 16 percent of these required additional evaluation.[38] The risk of perforation for CT colongraphy is estimated at 0 to 6 per 10,000 procedures.[6]

FECAL DNA TESTING

Genetic alterations that occur in the transition from adenoma to carcinoma can be extracted from stool samples and amplified to identify genetic mutations. A large prospective study compared fecal DNA testing with standard FOBT in 5,486 persons and found that fecal DNA testing was four times more sensitive than FOBT for detecting invasive cancer and twice as sensitive for detecting adenomatous polyps with high-grade dysplasia.[40] Also, patients have been shown to prefer fecal DNA testing to FOBT and colonoscopy.[41]

PILLCAM COLON

Pillcam Colon involves ingestion of a capsule that wirelessly acquires colonic images for later viewing. Two small studies (n = 132) have compared Pillcam Colon with colonoscopy.[42,43] The sensitivity and specificity of Pillcam Colon was inferior to that of colonoscopy for detection of polyps (sensitivity of 56 to 77 percent, specificity of 69 to 70 percent).[42,43] In both studies, a complete bowel preparation was required before the procedure.

Primary and Secondary Prevention

OBESITY

A large cohort study showed an association between increasing body mass index (BMI) and the relative risk of colorectal cancer mortality.[44] The relative risk of dying from colorectal cancer was 1.8 (95% CI, 1.4 to 2.4) in men with a BMI of 35.0 to 39.9 kg per m^2 compared with men of a healthy weight, and the relative risk of dying from colorectal cancer was 1.4 (95% CI, 1.06 to 1.74) in women with a BMI of 35.0 to 39.9 kg per m^2 compared with women of a healthy weight. Whether weight loss in adults who are obese or overweight prevents colon cancer is unknown.

FAT INTAKE

An analysis of 13 case-control studies did not find an association between fat intake and the risk of colorectal cancer[45]; however, there is evidence that high fat intake increases the risk of developing adenomatous polyps.[46]

RED MEAT

There is conflicting evidence about red meat and colorectal cancer risk. A large epidemiologic study found no association between red meat consumption and the risk of colorectal cancer mortality.[47] However, another large epidemiologic study did find an association between red meat consumption and increased incidence of colon cancer in women.[48]

FIBER

A systematic review failed to show any benefit of increased dietary fiber intake for reducing incidence or recurrence of adenomatous polyps.[49] This review reported findings of five studies involving 4,349 persons. There was no difference in fiber supplementation versus control groups (placebo or general dietary counseling) in decreasing the risk of adenomatous polyps (RR = 1.04; 95% CI, 0.95 to 1.13). Fiber should not be recommended to decrease the risk of colorectal cancer.

ASPIRIN, NSAIDS, AND COX–2 INHIBITORS

A USPSTF report found that, although aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) appear to

be effective at reducing the incidence of colonic adenomatous polyps and colorectal cancer, increased harms, such as gastrointestinal bleeding (with aspirin, NSAIDs, and cyclooxygenase-2 [COX-2] inhibitors), renal impairment (with NSAIDs and COX-2 inhibitors), and potentially increased cardiovascular risk (with COX-2 inhibitors), should be considered before recommending these agents for chemoprevention.[50] However, there is poor evidence that using these agents reduces colorectal cancer mortality. Thus, the USPSTF recommends against using them for chemoprevention in average-risk persons.[50]

CALCIUM

A Cochrane systematic review reported a modest reduction (odds ratio = 0.74; 95% CI, 0.58 to 0.95) in recurrent colorectal adenomatous polyps with calcium supplementation based on two studies with 1,346 persons.[51] However, there was insufficient evidence to recommend the general use of calcium supplementation to prevent colorectal cancer.

VITAMIN D

Vitamin D alone or combined with calcium may reduce the risk of colorectal cancer.[52] However, an analysis of 20 case-control and cohort studies found little evidence to support vitamin D as chemoprevention to decrease the risk of colorectal cancer.[53]

HORMONE THERAPY IN WOMEN

Two meta-analyses of mostly observational cohort studies of poor to good quality reported a 20 to 30 percent reduction in colon cancer incidence in women who had ever used hormone therapy.[54,55] There is contradictory evidence regarding whether hormone therapy reduces the risk of rectal cancer.[54,55] Data analyzed from the Women's Health Initiative study showed that, although women were at decreased risk of developing colon cancer, those women who did develop colon cancer were diagnosed at a more advanced stage than women who took placebo.[56]

ANTIOXIDANTS

A high-quality meta-analysis of eight trials including 17,260 persons found that, compared with no treatment or placebo, there was no benefit of antioxidants (beta-carotene, vitamin A, vitamin C, vitamin E, or selenium) in decreasing the risk of colorectal cancer.[57] Vitamin E was found to increase the risk of adenomatous polyps. Antioxidants should not be recommended to decrease the risk of colorectal cancer.

STATINS

A population-based case-control study found that colorectal cancer was 30 percent less likely to occur in patients who took a statin (simvastatin [Zocor] and pravastatin [Pravachol] were the most common statins in this study) for a least five years.[58] Data from randomized controlled trials are needed before statins can be recommended for primary prevention of colorectal cancer.

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