

Narrative Review: Screening for Colorectal Cancer in Patients with a First-Degree Relative with Colonic Neoplasia

Glenn M. Eisen, MD, MPH, and David S. Weinberg, MD, MSc

Many patients and providers are aware that colorectal cancer (CRC) "runs in families." A patient with 1 first-degree relative with CRC has approximately twice the personal risk for CRC as a similar person without this family history. Colorectal cancer is the third most common type of cancer in the United States. When providers neglect to collect information on family history, they may fail to appropriately tailor recommendations for screening for CRC for many patients.

This review considers the existing data and summarizes an evidence-based approach to the common clinical problem of how

and when to implement screening for CRC in a patient with a family history of colonic neoplasia. The authors discuss the varying risks for CRC given the patient's age, health habits, and personal and family histories. In the context of a clinical case that focuses on the effect of a single affected first-degree relative, the authors weigh the risks and benefits of various screening alternatives and briefly address chemoprevention, genetic testing, and future directions in screening for CRC.

Ann Intern Med. 2005;143:190-198.

For author affiliations, see end of text.

www.annals.org

A 48-year-old woman presents to her general internist to discuss screening for colorectal cancer (CRC). She has read several articles and news reports in the lay press related to the importance of this screening, and she would like to know more. She asks whether she should have CRC screening.

WHY DOES SCREENING REDUCE THE EFFECT OF COLORECTAL CANCER?

With an estimated 147 000 incident cases and 57 000 deaths in 2004, CRC is the third most common type of cancer and the second leading cause of cancer-associated death in the United States (1). Women and men are equally affected. Overall, about 1 in 20 adults will develop CRC (2). Most cases of CRC arise from adenomatous polyps. The visible progression from adenoma to cancer is accompanied by the accumulation of a series of genetic mutations (3). This process is believed to take 5 to 10 years (4), allowing a wide window of opportunity for intervention. Unlike screening for most other major types of cancer in humans, screening for CRC offers the real possibility of prevention rather than just early detection. Periodic screening for CRC reduces not only deaths from CRC but also disease incidence. Presumably, this benefit stems from the early detection and removal of polyps, as well as the detection of asymptomatic, early-stage cancer (5–7).

HOW DOES FAMILY HISTORY AFFECT SCREENING RECOMMENDATIONS?

The incidence of CRC begins to increase notably around age 50 years, and many authorities recommend that screening begin at that age for persons at average risk for CRC (8–10). Average risk is assumed to exist for anyone without signs or symptoms suggestive of CRC, without a personal or family history of colonic neoplasia (cancer or adenomatous polyps), and without any concomitant diseases that might increase risk (Table 1). Because CRC is

common, data on family history should always be obtained before a decision on screening is made. The following information on family history should be collected from patients.

1. The age at diagnosis of any first-degree relative affected by CRC or adenomatous polyps. In addition, the number of affected relatives, the number of polyps or tumors, and the location of the lesions are important.

2. When first-degree relatives are affected, especially at a young age (that is, with CRC before age 50 years or with colonic adenomas before age 45 years), an expanded history, including second-degree or more distant relatives, is useful. This is because CRC syndromes, including hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP), should be considered.

3. A family history not only of CRC but also of other HNPCC-related cancer (for example, endometrial, ovarian, gastric, and urinary tract cancer) should be elicited.

Awareness is growing among the general population about the effect of CRC. Demand for colonoscopy increased, for example, after *The Today Show* did a series on CRC (11). Although a family history of CRC is associated with greater participation in screening (12), screening rates remain persistently low in the United States despite changes in public awareness and greater willingness by insurers to cover the costs of screening (13).

The patient states that she has no gastrointestinal symptoms except for occasional reflux. Her only medication is acetaminophen, as needed, for occasional headaches. She does state

See also:

Web-Only

CME quiz

Conversion of tables into slides

that her father had several colon polyps first diagnosed at age 52 years. No one else in her family has a history of polyps or CRC.

DOES THIS PATIENT'S FAMILY HISTORY JUSTIFY SCREENING FOR COLORECTAL CANCER BEFORE AGE 50 YEARS?

Having a first-degree relative with adenomatous colon polyps before age 60 years elevates the patient's risk sufficiently to warrant screening now, rather than waiting until she reaches age 50 years (8). Many patients and providers are aware that CRC "runs in families." Colorectal cancer in 1 first-degree relative nearly doubles a patient's personal risk for CRC (the lifetime risk in the general population is 5% to 6%) (14). In persons with a single affected first-degree relative, the incidence of CRC at age 40 years is similar to the incidence of CRC at age 50 years in persons without a family history of CRC. Risk increases with the number of affected relatives and is especially magnified when affected family members develop CRC at a young age (that is, before age 50 years).

Providers may neglect to collect complete information on family history of cancer from their patients (15). Although adenomatous polyps affect risk less than CRC does, the same concerns apply when a first-degree relative is affected. The relative risk for CRC in parents and siblings of patients with adenomas is 1.8 (95% CI, 1.2 to 2.7) compared with controls. It increases to 2.6 (CI, 1.5 to 4.6) if the affected family member is younger than 60 years of age at the time of polyp detection (16). The effect of a family history of adenomatous polyps is underestimated by the public (17) and by health care providers (18, 19).

It is important to note that risk-assessment studies often include persons with large or symptomatic polyps. Extrapolating data on these patients to the more common scenario of the patient with a first-degree relative with smaller polyps is difficult. In most cases, if patients are aware that family members had polyps, they are uncertain about whether the polyps were adenomatous or hyperplastic. In the absence of specific information, most experts would assume that risk is increased and promote early screening in these patients, given the potential benefit of cancer prevention weighed against the modest risk associated with screening.

Although the recommendations are not based on prospective studies, most authorities recommend that these patients begin screening at age 40 years (or 10 years before the earliest diagnosed case in the immediate family) rather than at age 50 years (8, 9, 20, 21) (Table 2). However, a substantial disparity exists between published recommendations and actual clinical practice. Recent survey data suggest that fewer than 50% of either gastroenterologists or primary care physicians routinely recommend screening beginning at age 40 years in this setting (18).

Table 1. Risk Factors for Colorectal Cancer

History of colorectal cancer or adenoma
One or more first-degree relatives with colorectal cancer or adenoma
Inflammatory bowel disease for >8 years (pancolitis) or >15 years (left-sided colitis)
Ovarian or endometrial cancer, particularly if diagnosed before age 60 years
Acromegaly
Ureterocolostomy

DOES THIS PATIENT'S HISTORY SUGGEST HEREDITARY NONPOLYPOSIS COLON CANCER OR FAMILIAL ADENOMATOUS POLYPOSIS?

The HNPCC syndrome is believed to develop because of mutation in 1 of several DNA mismatch repair genes. Mutation carriers have greater risk for cancer of the ovary, uterus, ureter, renal pelvis, stomach, small bowel, and bile duct than does the unaffected population. Without intervention, 80% of persons with HNPCC develop CRC by age 50 years. Phenotypically, these cases of CRC are more likely than sporadic CRC to arise in the proximal colon. Several diagnostic criteria for HNPCC have been suggested. The Amsterdam or Bethesda criteria are used most often, although the weaknesses of these systems are widely acknowledged (22).

In contrast, FAP is characterized by early development of diffuse colonic polyps; in some cases, thousands of adenomas are seen. Mutation in the APC gene lies at the heart of this syndrome, which represents no more than 1% of all cases of CRC. Without intervention, nearly 100% of persons with FAP will develop CRC by about age 40 years. Attenuated FAP, a variant of this syndrome, is characterized by fewer polyps and later onset of cancer. Other phenotypic features associated with FAP are small-bowel adenomas (with an attendant increase in risk for cancer, particularly periampullary carcinoma), desmoid tumors, osteoma, dental abnormalities, and a variety of additional extraintestinal manifestations.

Recognizing hereditary CRC syndromes, such as HNPCC or FAP, can be challenging. When eliciting family history, the health care provider should devote particular attention to identifying first- or second-degree relatives who had CRC before age 50 years, adenomas before age 45 years, or large numbers of adenomas (>10). In addition, information on the types of extracolonic cancer associated with HNPCC should be sought. These types of cancer may develop in the absence of CRC in some family members. Referral to centers that are equipped to provide molecular diagnostic testing and genetic counseling should be considered for all patients and families if HNPCC or FAP is a possibility. More complete discussions of FAP, HNPCC, and associated testing issues can be found in several recent reviews (23, 24). Overall, the absence of any of the clinical features associated with FAP or HNPCC makes it unlikely that the patient is a member of an affected kindred.

Table 2. Screening Recommendations for Persons with Various Family Histories*

Family History	Screening Recommendation
Familial adenomatous polyposis with positive result on a genetic test in proband	Offer genetic testing with counseling; if test results are positive, annual FS beginning at age 10 to 12 years with colectomy when polyps develop. If no polyps are seen on annual FS to age 40 years, then do FS every 3 to 5 years thereafter (some experts would substitute colonoscopy for FS).
Familial adenomatous polyposis with negative result on a genetic test in proband	FS in all potentially affected relatives beginning at age 10 to 12 years with colectomy when polyps develop. If no polyps are seen on annual FS to age 40 years, then do FS every 3 to 5 years thereafter (some experts would substitute colonoscopy for FS).
Hereditary nonpolyposis colon cancer	Colonoscopy beginning at age 25 years or 5 years before the earliest age of diagnosis of CRC, whichever is earlier. Annual screening after age 40 years.
First-degree relatives with sporadic CRC or adenomas before age 60 years or more than 1 first-degree relative with CRC or adenomas	Colonoscopy beginning at age 40 years, or 10 years before the age at diagnosis of the youngest affected relative. If the results are normal, repeat colonoscopy at 5-year intervals.
First-degree relative with CRC or adenomatous polyp diagnosed after age 60 years or 2 second-degree relatives with CRC	Use screening recommendations for average-risk persons, but begin screening at age 40 years.

* CRC = colorectal cancer; FS = flexible sigmoidoscopy.

The patient agrees to have screening for CRC.

WHAT SCREENING PROCEDURE IS APPROPRIATE FOR THIS PATIENT?

For most of the general population, no consensus exists to support a particular method of screening for CRC. Instead, health care providers have been urged to concentrate on increasing rates of screening among their patients through periodic use of any of the recommended techniques: fecal occult blood testing, flexible sigmoidoscopy, air-contrast barium enema, or colonoscopy (9, 10). In the setting described in this paper, an explicit recommendation for colonoscopy represents a clear break from CRC screening guidelines for persons at average risk. Primary care physicians may not be aware of this important difference (18).

No randomized trials have shown that periodic colonoscopy leads to a reduction in CRC-related deaths. However, a wealth of indirect evidence has resulted in the ascendance of colonoscopy as the de facto gold standard for CRC screening. For example, the randomized trials of fecal occult blood testing that did show a reduction in CRC incidence and CRC-related death used colonoscopy to evaluate patients with a positive result on stool guaiac testing. The National Polyp Study showed that colonoscopy with removal of all visible polyps resulted in a 75% to 90% reduction in the predicted incidence of CRC (25). However, this study used historical controls, and all patients in the study had polypectomy; therefore, the results may not be free of bias. A case-control study done in the Veterans Administration setting by Muller and Sonnenberg (26) found that patients who had previously had colonoscopy had a lower odds ratio (OR) for CRC-related death (OR,

0.43 [CI, 0.30 to 0.63]). Most recently, 2 prospective studies of colonoscopy screening in persons at average risk who were 50 years of age or older (27, 28) found that one half of cases of advanced proximal neoplasia would be missed if only sigmoidoscopy was done.

Colonoscopy does offer the advantages of complete visualization of the entire colon coupled with therapeutic potential. In patients at elevated risk for CRC, various authorities have considered the available evidence and concluded that colonoscopy is the test of choice. However, the procedure is more expensive than other screening tests and has a greater potential for adverse events. It usually involves the use of conscious sedation, which itself entails risk as well as loss of time from the workplace. Two recent studies of colonoscopy screening have provided a prospective assessment of potential complications. Imperiale and coworkers (27) found a 0.5% perforation rate (1 of 1994) and 3 cases of postprocedural bleeding that necessitated visits to emergency departments. Lieberman and associates (28) found a major complication rate of 0.3% (10 of 3121), which included 6 cases of bleeding requiring hospitalization. No perforations were seen, but 3 patients died within 1 month of the procedure (none of the deaths were believed to be related to the procedure). Overall, perforation rates seem to be between 0.2% and 0.7% and bleeding rates between 0.2% and 3.0% (the higher percentage applies if polypectomy is done) (29). Deaths related to colonoscopy screening are rare and difficult to quantify. A recent decision model estimated the rate as 1 in 20 000 (30).

Air-contrast barium enema is recommended when colonoscopy is not available or is declined. However, this

substitution should be minimized, particularly in groups with a family history of CRC, adenomas, or both. Air-contrast barium enema has not been studied as a screening test for CRC in randomized trials. A recent head-to-head comparison of air-contrast barium enema and colonoscopy (31) showed that barium enema detected 32% of polyps less than 5 mm in size, 53% of polyps 6 mm to 10 mm in size, and only 48% of those greater than 1 cm in size. A recent prospective study (32) found that the sensitivity for detecting CRC was 83% for barium enema radiography compared with 95% for colonoscopy. Air-contrast barium enema is included as a screening option because it can evaluate the entire colon and is widely available. However, it is clearly less sensitive than colonoscopy, and colonoscopy is necessary if air-contrast barium enema shows a probable lesion. The risk for serious adverse events with barium enema is low. A U.K. survey (33) of barium enema (for any indication, not just screening) over a 3-year period showed a perforation rate of 1 in 25 000, 1 death in 55 000 (not clearly related to barium enema), and an overall complication rate of 1 in 10 000 examinations.

The addition of flexible sigmoidoscopy to air-contrast barium enema could be considered because of the poor visualization of the rectosigmoid colon obtained with air-contrast barium enema alone. However, no prospective studies have shown the efficacy of screening done using barium enema for reducing CRC-related mortality rates. Whether flexible sigmoidoscopy adds benefit remains unclear.

On the basis of this information, you recommend colonoscopy; however, the patient is reluctant. Recognizing the shortcomings of air-contrast barium enema, she wants to know about other options, such as virtual colonoscopy or blood- or stool-based testing.

HOW WOULD YOU COUNSEL THIS PATIENT ABOUT VIRTUAL AND CONVENTIONAL COLONOSCOPY?

Computed tomographic (and magnetic resonance imaging) colography, or virtual colonoscopy, has recently been widely discussed as a potential tool for CRC screening. The potential advantages of virtual colonoscopy include no requirement for sedation and minimal invasiveness. Early studies suggest that radiologists interpreting virtual colonoscopy studies face a steep learning curve. Not surprisingly, results have varied significantly by center. Overall, the sensitivity for lesions 1 cm or larger has ranged from approximately 30% to more than 90%, with considerably lower sensitivities for smaller lesions (34–37). Conventional colonoscopy was the gold standard with which virtual colonoscopy (and, historically, other screening tests) was compared. The advent of virtual colonoscopy shows how this standard may be somewhat tarnished. Conventional colonoscopy seems, on initial visualization, to miss about 10% of polyps 10 mm or more in diameter that are

detected by virtual colonoscopy and then seen with conventional colonoscopy on directed “re-look” (38). In addition to further confusing data interpretation, this deficiency should remind providers and patients of the fallibility of any screening test.

Where virtual colonoscopy will be most useful is unclear. Low sensitivity, especially for smaller polyps, has been seen as a substantial fault that needs to be overcome. This is true if the absolute ability to discern individual polyps is crucial. Conversely, if the goal of screening with virtual colonoscopy is to identify at least 1 polyp, since such a finding will trigger use of conventional colonoscopy, then sensitivity requirements might be relaxed. An early cost-effectiveness analysis comparing virtual colonoscopy and colonoscopy for CRC screening (39) suggested that virtual colonoscopy would need to have 15% to 20% better compliance or 54% less cost than colonoscopy to be considered equally cost-effective. Of particular relevance to screening in patients with a family history of CRC, a more recent study concluded that as the likelihood of colonic neoplasia increased, the cost-effectiveness of virtual colonoscopy decreased. Presumably, this is due to the costs associated with a positive result on virtual colonoscopy, which necessitates subsequent conventional colonoscopy for polypectomy (40). An additional concern is the incidental detection by virtual colonoscopy of extracolonic abnormalities that may have no clinical significance. Further work-up of patients with these results may lead to unnecessary and expensive diagnostic testing and even surgery (41).

For many patients, the greatest barrier to colonoscopy is the preparatory laxative purge. Virtual colonoscopy without such cathartics has been described (42), but virtual colonoscopy currently requires the same preparation as conventional colonoscopy for optimal image quality. Preliminary data on the use of stool tagging could potentially eliminate patient preparation and increase acceptance (43). Further clinical validation testing is necessary before virtual colonoscopy is endorsed as a screening tool.

COULD SCREENING WITH STOOL-BASED MARKERS BE USEFUL IN PATIENTS WITH ELEVATED RISK FOR COLORECTAL CANCER?

Currently, the only stool-based test recommended for CRC screening is the fecal occult blood test. Although this test is cost-effective, its usefulness is sharply limited by poor sensitivity unless it is used repeatedly over time. Development of a reliable, noninvasive, stool-based screening method holds considerable appeal. The technology of a stool-based screening method is based on the concept that exfoliated cancer cells in the fecal stream may reflect many of the genetic alterations associated with CRC. More than 10 years ago, the possibility of assessing k-ras in the stool was examined (44). Although the testing was feasible, this marker alone was not sufficient because most CRC does

Table 3. Surveillance Recommendations for Persons with Important Personal History

Personal History	Surveillance Recommendation
Previous colorectal cancer	Clearance of the remainder of the colon at or around the time of resection, followed by colonoscopy at 3 years after curative resection and then at 3- to 5-year intervals to detect metachronous neoplasia
Previous colonic adenomas	After adequate clearance, surveillance colonoscopy at 3- to 5-year intervals
Ulcerative proctocolitis, Crohn proctocolitis of 8 years' duration, or left-sided colitis of more than 15 years' duration	Surveillance colonoscopy every 1 to 3 years with systematic biopsies to detect dysplasia

not express mutated k-ras. More recently, stool-based molecular testing has become available that assays numerous targets, including APC, k-ras, p53, BAT-26, and more general assessment of DNA fragment length. Published trials using the multiple target approach (45–47) describe sensitivity for cancer between 63% and 91% and sensitivity for adenomatous polyps between 57% and 82%. More recently, the results of a large, multicenter trial comparing fecal DNA testing with fecal occult blood testing and colonoscopy for the detection of CRC and advanced adenomas were released. Although fecal DNA testing was more likely than fecal occult blood testing to identify invasive cancer (52% compared with 13% of colonoscopy-verified cases; $P < 0.05$), neither stool-based test identified most important neoplastic lesions (tumors ≥ 1 cm or dysplastic adenomas) (48). Currently, fecal DNA testing remains an intriguing but unproven technology.

WHEN MIGHT GENETIC TESTING BE USEFUL IN PATIENTS WITH A FAMILY HISTORY OF COLORECTAL CANCER?

To date, genetic testing for CRC is limited to clinical situations suggestive of HNPCC or FAP. Genetic testing is typically recommended either to confirm a suspected diagnosis of an inherited CRC syndrome or to document carrier status if a mutation has already been identified in a particular family (49). At present, no specific mutations have been identified that reliably predict risk for CRC outside of the HNPCC or FAP settings. However, there has been a growing effort to assess susceptibility to cancer in healthy persons by assessing genetic and epigenetic phenomena associated with risk for cancer. For example, Cui and colleagues (50) evaluated blood and colon tissue biopsies for loss of imprinting of the insulin-like growth factor II gene. This gene is normally imprinted by methylation, and loss of imprinting leads to increased expression of the gene. Insulin-like growth factor II regulates cellular growth and differentiation in many tissues. Loss of imprinting of the gene was associated with both a family history of CRC and a personal history of adenomatous polyps and CRC.

Additional modestly predictive associations between CRC and other genetic markers appear with increasing frequency in the literature (51). Such individualized testing may become important if future risk for CRC could be predicted with reasonable accuracy. Individuals with lower risk could potentially avoid invasive testing, such as colonoscopy, while those with higher risk could be targeted for more aggressive screening.

The patient chooses to have colonoscopy. The examination reveals 2 polyps, the larger being 1 cm in diameter. The pathology report indicates that the larger polyp is a tubular adenoma and the smaller polyp is hyperplastic. The patient wishes to know if and when she will need further testing and whether she can do anything to limit recurrence of these polyps.

WITH WHAT FREQUENCY SHOULD COLONOSCOPIC SCREENING BE DONE IN PATIENTS WITH POLYPS?

The size, number, and histologic characteristics of polyps influence the length of the interval between surveillance colonoscopies. Given that the patient had a single, 1-cm adenomatous polyp, current recommendations suggest doing another colonoscopy in 3 to 5 years (Table 3). Evidence from randomized, controlled trials (52) shows similar detection rates for advanced lesions when colonoscopy is done at 3-year and 1-year intervals. Advanced lesions are defined as adenomatous (as opposed to hyperplastic) polyps 1 cm or more in size or adenomas with histologic dysplasia. The rationale for surveillance examination is 2-fold: to find lesions missed on the index colonoscopy and to detect further advanced lesions. Persons with lesions smaller than 1 cm (also without advanced histologic features) require less frequent surveillance, and current recommendations suggest that these patients have a follow-up examination at 5 years, even with a family history of CRC. Data suggest that the index examination is most beneficial and that subsequent examinations may add little except in patients at high risk for advanced lesions (53). A recent survey (54) suggests that surveillance colonoscopy is done more frequently than currently advocated. While recommendations about surveillance examinations continue to evolve, it is unlikely that the typical interval between procedures will be reduced.

CAN FUTURE RISK FOR POLYPS OR CANCER BE REDUCED?

No controlled trials have specifically investigated the protective effects of diet, lifestyle choices, or chemoprevention on risk for familial CRC. However, the increased risk associated with family history is a compelling reason for affected persons and their physicians to consider the usefulness of information about risk reduction extrapolated from studies of populations at average risk and populations with FAP.

The role of diet in CRC remains controversial. Equally uncertain is the practical issue of the effect of dietary change on risk for CRC. Many studies support the belief that diets high in fruits and vegetables and low in animal fats offer some protection against CRC in average-risk populations. However, it is unclear which dietary constituents (vitamins, fiber, micronutrients) are beneficial. A standard belief is that high-fiber diets reduce risk for CRC; this belief is based on studies showing lower risk for cancer in populations that regularly consume greater amounts of fiber (55). However, in most instances, interventions intended to prevent disease emphasize how to change (that is, improve) diet to minimize risk. Recent studies have shown little effect of high-fiber diets on secondary prevention of colorectal neoplasia, and specifically on reduction in polyp recurrence rates (56, 57). Fiber is simply one element for which evidence is lacking to show that dietary change reduces the risk for cancer.

Any discussion of diet needs to consider the related issue of obesity. Substantial evidence suggests that increasing obesity is directly related to risk for CRC, whereas exercise is inversely related to this risk (58). As with diet, a relationship may exist, but the mechanism is unknown. At present, prudent advice about diet and CRC would probably emphasize the overall health benefits of healthy food choices in moderation, coupled with regular exercise.

A variety of agents has been studied as potential chemopreventive factors for persons at average risk for CRC. Such agents as vitamins A, C, and E or selenium possess antioxidant abilities. Despite their theoretical usefulness, however, none has reproducibly shown any substantial benefit in the prevention of colonic neoplasia (59). The role of vitamin D, to date, has been inconsistent (60). More promising is long-term supplemental intake of calcium or folate. Calcium supplementation seems to protect against the development of distal (but perhaps not proximal) CRC and against recurrence of colorectal polyps after colonoscopic polypectomy (61, 62). In both instances, risk reductions were modest but important. In long-term studies, folate supplementation equivalent to that provided by a standard multivitamin substantially reduces risk for CRC. However, this benefit, at least in average-risk persons, is greatest after 10 or more years of regular folate intake (63).

Numerous observational and case-control studies have documented the protective effect of hormone replacement therapy against CRC in women. Meta-analyses suggest a 20% reduction in risk for CRC, particularly for long-term and current users of hormone replacement therapy (64). Results from the prospective Women's Health Initiative trial (65) showed a 40% reduction in risk for CRC for users of hormone replacement therapy compared with nonusers. However, this trial also documented unwanted side effects of hormone replacement therapy, including increased risk for breast cancer and no apparent cardioprotective effect. Currently, the U.S. Preventive Services Task Force (66) recommends against the use of hormone re-

placement therapy because overall risk seems to exceed benefit.

The observation that sulindac, a nonsteroidal anti-inflammatory drug, caused partial regression of existing polyps in patients with FAP has spurred extensive investigation of this class of drugs as a potential chemopreventive agent in CRC. Nonsteroidal anti-inflammatory drugs have myriad antineoplastic effects mediated, at least in part, by inhibition of different isoforms of cyclooxygenase, an enzyme that facilitates conversion of arachidonic acids into a variety of bioactive substances that can promote carcinogenesis. Expression of cyclooxygenase-2 is increased in as many as 90% of cases of CRC and in more than 50% of cases of colonic adenoma.

Several observational studies have documented a protective effect for regular users of aspirin (a nonselective cyclooxygenase inhibitor) at average risk for CRC. As with folate, multiyear use may be necessary to generate the greatest effect. Two recent randomized trials (67, 68) have shown the protective effect of aspirin in preventing colorectal adenomas. One trial randomly assigned more than 1000 patients, after clearing colonoscopy, to receive placebo, low-dose (81-mg) aspirin, or regular-strength (325-mg) aspirin. Low-dose aspirin was found to reduce the subsequent risk for any adenoma (relative risk, 0.81 [CI, 0.69 to 0.96]) and advanced neoplasms (adenomas > 1 cm or advanced histologic features) (relative risk, 0.59 [CI, 0.38 to 0.92]). The second trial involved a high-risk population: patients with CRC, 635 of whom were randomly assigned to receive 325 mg of aspirin or placebo. At least 1 adenoma was subsequently found in 17% of the aspirin group and 27% of the placebo group ($P = 0.004$). The authors cautioned all patients against starting aspirin therapy to protect against CRC because of the risks for bleeding associated with this therapy.

More recently, the cyclooxygenase-2-specific inhibitor celecoxib was shown to reduce the number and size of existing adenomas in patients with FAP, although the drug was less efficacious when used to prevent primary polyps in similar patients. No data specifically support the use of cyclooxygenase-2-specific inhibitors, in contrast to nonselective inhibitors. Recent cost-effectiveness analyses found colonoscopic screening to be more effective and less costly than aspirin or celecoxib for preventing CRC (69, 70). This information, coupled with ongoing concerns about excess cardiovascular risk associated with use of cyclooxygenase-2 inhibitors, contributes to the uncertain role of these inhibitors as regular interventions at the population level (71, 72).

At present, no firm evidence supports the use of specific chemoprevention agents for persons at average risk for CRC or persons with a family history of the disease. For persons eager to pursue methods to reduce their chances of CRC, it may be reasonable to suggest increased regular intake of folate, calcium, or both. Folate and calcium both provide additional health benefits and, with rare excep-

tions, present low risk when consumed in moderate doses (73, 74). It may also be reasonable to consider the regular use of low-dose aspirin, especially in persons who may also derive cardioprotection from this therapy, although the risks associated with bleeding need to be carefully considered (75).

SUMMARY

Colorectal cancer is an important cause of cancer-related illness and death in the United States. A person at average risk is encouraged to begin screening for CRC at age 50 years. Currently accepted choices for average-risk persons include fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, and barium enema. Persons with familial syndromes, such as FAP or HNPCC, clearly require early and intensive CRC screening with colonoscopy. However, these familial syndromes account for only about 5% of cases of CRC (76). Practitioners need to actively elicit a patient's family history for both CRC and adenomatous polyps because the presence of either increases risk for CRC. At this time, colonoscopy is the accepted screening method for patients with a positive family history. Exciting new developments in CRC screening include molecular-based blood and stool tests, as well as virtual colonoscopy. However, these are not yet ready for widespread use. Chemopreventive efforts have yet to produce sufficient benefit to merit broad adoption.

From Oregon Health and Science University, Portland, Oregon, and Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: David S. Weinberg, MD, MSc, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111; e-mail, david.weinberg@fccc.edu.

Current author addresses are available at www.annals.org.

References

- Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer statistics, 2004. *CA Cancer J Clin*. 2004;54:8-29. [PMID: 14974761]
- Ris LA, Miller BA, Hankey BF, eds. *SEER Cancer Statistics Review 1973-1991*. NIH pub. no. 94-2789. Bethesda, MD: National Cancer Institute; 1994.
- Kinzler KW, Vogelstein B. Colorectal tumors. In: Vogelstein B, Kinzler KW, eds. *The Genetic Basis of Human Cancer*. New York: McGraw-Hill; 1998:565-87.
- Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology*. 1987;93:1009-13. [PMID: 3653628]
- Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993;328:1365-71. [PMID: 8474513]
- Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348:1472-7. [PMID: 8942775]
- Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996;348:1467-71. [PMID: 8942774]
- Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal

- cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology*. 2003;124:544-60. [PMID: 12557158]
- Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2004. *CA Cancer J Clin*. 2004;54:41-52. [PMID: 14974763]
 - Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2002;137:132-41. [PMID: 12118972]
 - Cram P, Fendrick AM, Inadomi J, Cowen ME, Carpenter D, Vijan S. The impact of a celebrity promotional campaign on the use of colon cancer screening: the Katie Couric effect. *Arch Intern Med*. 2003;163:1601-5. [PMID: 12860585]
 - Slattery ML, Kinney AY, Levin TR. Factors associated with colorectal cancer screening in a population-based study: the impact of gender, health care source, and time. *Prev Med*. 2004;38:276-83. [PMID: 14766109]
 - Seeff LC, Nadel MR, Klabunde CN, Thompson T, Shapiro JA, Vernon SW, et al. Patterns and predictors of colorectal cancer test use in the adult U.S. population. *Cancer*. 2004;100:2093-103. [PMID: 15139050]
 - Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med*. 1994;331:1669-74. [PMID: 7969357]
 - Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. *Am J Prev Med*. 2004;27:239-45. [PMID: 15450637]
 - Winawer SJ, Zauber AG, Gerdes H, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. *N Engl J Med*. 1996;334:82-7. [PMID: 8531963]
 - Schroy PC 3rd, Lal SK, Wilson S, Heeren T, Farraye FA. Deficiencies in knowledge and familial risk communication among colorectal adenoma patients. *J Clin Gastroenterol*. 2005;39:298-302. [PMID: 15758623]
 - Schroy PC 3rd, Barrison AF, Ling BS, Wilson S, Geller AC. Family history and colorectal cancer screening: a survey of physician knowledge and practice patterns. *Am J Gastroenterol*. 2002;97:1031-6. [PMID: 12008667]
 - Barrison AF, Smith C, Oviedo J, Heeren T, Schroy PC 3rd. Colorectal cancer screening and familial risk: a survey of internal medicine residents' knowledge and practice patterns. *Am J Gastroenterol*. 2003;98:1410-6. [PMID: 12818289]
 - Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol*. 2000;95:3053-63. [PMID: 11095318]
 - National Comprehensive Cancer Network. Colorectal cancer screening guidelines. Accessed at www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf on 6 June 2005.
 - Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology*. 1999;116:1453-6. [PMID: 10348829]
 - Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. *Ann Intern Med*. 2003;138:560-70. [PMID: 12667026]
 - Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology*. 2001;121:198-213. [PMID: 11438509]
 - Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993;329:1977-81. [PMID: 8247072]
 - Muller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. *Arch Intern Med*. 1995;155:1741-8. [PMID: 7654107]
 - Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med*. 2000;343:169-74. [PMID: 10900275]
 - Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Gawarek H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000;343:162-8. [PMID: 10900274]
 - Guidelines for colorectal cancer screening and surveillance. *Gastrointest Endosc*. 2000;51:777-82. [PMID: 10840334]

30. Wagner J, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average risk adults. In: Young G, Rozen P, Levin B, eds. *Prevention and Early Detection of Colorectal Cancer*. London: Saunders; 1996:321-56.
31. Winawer SJ, Stewart ET, Zauber AG, Bond JH, Ansel H, Waye JD, et al. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med*. 2000; 342:1766-72. [PMID: 10852998]
32. Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. *Gastroenterology*. 1997;112:17-23. [PMID: 8978337]
33. Blakeborough A, Sheridan MB, Chapman AH. Complications of barium enema examinations: a survey of UK Consultant Radiologists 1992 to 1994. *Clin Radiol*. 1997;52:142-8. [PMID: 9043049]
34. Johnson CD, Harmsen WS, Wilson LA, Maccarty RL, Welch TJ, Ilstrup DM, et al. Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterology*. 2003;125:311-9. [PMID: 12891530]
35. Pineau BC, Paskett ED, Chen GJ, Espeland MA, Phillips K, Han JP, et al. Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology*. 2003;125:304-10. [PMID: 12891529]
36. Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003;349:2191-200. [PMID: 14657426]
37. Cotton PB, Durkalski VL, Pineau BC, Palesch YY, Mauldin PD, Hoffman B, et al. Computed tomographic colonography (virtual colonoscopy): a multi-center comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA*. 2004;291:1713-9. [PMID: 15082698]
38. Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Ann Intern Med*. 2004;141:352-9. [PMID: 15353426]
39. Sonnenberg A, Delco F, Bauerfeind P. Is virtual colonoscopy a cost-effective option to screen for colorectal cancer? *Am J Gastroenterol*. 1999;94:2268-74. [PMID: 10445561]
40. Ladabaum U, Song K, Fendrick AM. Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? *Clin Gastroenterol Hepatol*. 2004;2:554-63. [PMID: 15224279]
41. Gluecker TM, Johnson CD, Wilson LA, Maccarty RL, Welch TJ, Vanness DJ, et al. Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. *Gastroenterology*. 2003;124:911-6. [PMID: 12671887]
42. Iannaccone R, Laghi A, Catalano C, Mangiapane F, Lamazza A, Schillaci A, et al. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. *Gastroenterology*. 2004;127:1300-11. [PMID: 15520999]
43. Pickhardt PJ, Choi JH. Electronic cleansing and stool tagging in CT colonography: advantages and pitfalls with primary three-dimensional evaluation. *AJR Am J Roentgenol*. 2003;181:799-805. [PMID: 12933484]
44. Sidransky D, Tokino T, Hamilton SR, Kinzler KW, Levin B, Frost P, et al. Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. *Science*. 1992;256:102-5. [PMID: 1566048]
45. Ahlquist DA, Skoletsky JE, Boynton KA, Harrington JJ, Mahoney DW, Pierceall WE, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology*. 2000; 119:1219-27. [PMID: 11054379]
46. Dong SM, Traverso G, Johnson C, Geng L, Favis R, Boynton K, et al. Detecting colorectal cancer in stool with the use of multiple genetic targets. *J Natl Cancer Inst*. 2001;93:858-65. [PMID: 11390535]
47. Tagore KS, Lawson MJ, Yucaitis JA, Gage R, Orr T, Shuber AP, et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. *Clin Colorectal Cancer*. 2003;3:47-53. [PMID: 12777192]
48. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med*. 2004;351:2704-14. [PMID: 15616205]
49. Giardiello FM. Genetic testing in hereditary colorectal cancer. *JAMA*. 1997; 278:1278-81. [PMID: 9333271]
50. Cui H, Cruz-Correa M, Giardiello FM, Hutcheon DF, Kafonek DR, Brandenburg S, et al. Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. *Science*. 2003;299:1753-5. [PMID: 12637750]
51. Houlston RS, Tomlinson IP. Polymorphisms and colorectal tumor risk. *Gastroenterology*. 2001;121:282-301. [PMID: 11487538]
52. Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med*. 1993;328:901-6. [PMID: 8446136]
53. Noshirvani KC, van Stolk RU, Rybicki LA, Beck GJ. Adenoma size and number are predictive of adenoma recurrence: implications for surveillance colonoscopy. *Gastrointest Endosc*. 2000;51:433-7. [PMID: 10744815]
54. Mysliwiec PA, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. *Ann Intern Med*. 2004;141:264-71. [PMID: 15313742]
55. Howe GR, Aronson KJ, Benito E, Castelletto R, Cornee J, Duffy S, et al. The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control*. 1997;8:215-28. [PMID: 9134246]
56. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med*. 2000;342:1149-55. [PMID: 10770979]
57. Alberts DS, Martinez ME, Roe DJ, Guillen-Rodriguez JM, Marshall JR, van Leeuwen JB, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. *N Engl J Med*. 2000;342:1156-62. [PMID: 10770980]
58. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625-38. [PMID: 12711737]
59. Patterson RE, White E, Kristal AR, Neuhauser ML, Potter JD. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control*. 1997;8:786-802. [PMID: 9328202]
60. McCullough ML, Robertson AS, Rodriguez C, Jacobs EJ, Chao A, Carolyn J, et al. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control*. 2003;14:1-12. [PMID: 12708719]
61. Martinez ME, Willett WC. Calcium, vitamin D, and colorectal cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev*. 1998; 7:163-8. [PMID: 9488592]
62. Hyman J, Baron JA, Dain BJ, Sandler RS, Haile RW, Mandel JS, et al. Dietary and supplemental calcium and the recurrence of colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*. 1998;7:291-5. [PMID: 9568783]
63. Giovannucci E, Stampfer MJ, Colditz GA, Hunter DJ, Fuchs C, Rosner BA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med*. 1998;129:517-24. [PMID: 9758570]
64. Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol*. 1999; 93(5 Pt 2):880-8. [PMID: 10912438]
65. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-33. [PMID: 12117397]
66. U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med*. 2002;137:834-9. [PMID: 12435221]
67. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003; 348:891-9. [PMID: 12621133]
68. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348:883-90. [PMID: 12621132]
69. Suleiman S, Rex DK, Sonnenberg A. Chemoprevention of colorectal cancer by aspirin: a cost-effectiveness analysis. *Gastroenterology*. 2002;122:78-84. [PMID: 11781283]
70. Arguedas MR, Heudebert GR, Wilcox CM. Surveillance colonoscopy or chemoprevention with COX-2 inhibitors in average-risk post-polypectomy patients: a decision analysis. *Aliment Pharmacol Ther*. 2001;15:631-8. [PMID: 11328256]
71. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colo-

rectal adenoma chemoprevention trial. *N Engl J Med.* 2005;352:1092-102. [PMID: 15713943]

72. **Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al.** Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005;352:1071-80. [PMID: 15713944]

73. **Fletcher RH, Fairfield KM.** Vitamins for chronic disease prevention in adults: clinical applications. *JAMA.* 2002;287:3127-9. [PMID: 12069676]

74. **Weisburger JH.** Lifestyle, health and disease prevention: the underlying mechanisms. *Eur J Cancer Prev.* 2002;11 Suppl 2:S1-7. [PMID: 12570328]

75. **Sandler RS.** Aspirin prevention of colorectal cancer: more or less? [Editorial] *Ann Intern Med.* 2004;140:224-5. [PMID: 14757621]

76. **Burt RW, Petersen GM.** Familial colorectal cancer: diagnosis and management. In: Young GP, Rozen P, Levin B, eds. *Prevention and Early Detection of Colorectal Cancer.* Philadelphia: WB Saunders; 1996:171-93.

Current Author Addresses: Dr. Eisen: Oregon Health and Science University, Mail Code PV310, 3181 SW Sam Jackson Park Road, Portland, OR 97239.

Dr. Weinberg: Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111.