8. Screening for Colorectal Cancer

RECOMMENDATION

Screening for colorectal cancer is recommended for all persons aged 50 and older with annual fecal occult blood testing (FOBT), or sigmoidoscopy (periodicity unspecified), or both (see *Clinical Intervention*). There is insufficient evidence to determine which of these screening methods is preferable or whether the combination of FOBT and sigmoidoscopy produces greater benefits than does either test alone. There is also insufficient evidence to recommend for or against routine screening with digital rectal examination, barium enema, or colonoscopy, although recommendations against such screening in average-risk persons may be made on other grounds (see *Clinical Intervention*). Persons with a family history of hereditary syndromes associated with a high risk of colon cancer should be referred for diagnosis and management (see *Clinical Intervention*).

Burden of Suffering

Colorectal cancer is the second most common form of cancer in the U.S. and has the second highest mortality rate, accounting for about 140,000 new cases and about 55,000 deaths each year.[1] An individual's lifetime risk of dying of colorectal cancer in the U.S. has been estimated to be 2.6%.[2] About 60% of patients with colorectal cancer have regional or distant metastases at the time of diagnosis.[1] Estimated 5-year survival is 91% in persons with localized disease, 60% in persons with regional spread, and only 6% in those with distant metastases.[2] The average patient dying of colorectal cancer loses 13 years of life.[2] In addition to the mortality associated with colorectal cancer, this disease and its treatment—surgical resection, colostomies, chemotherapy, and radiotherapy—can produce significant morbidity. Persons at highest risk of colorectal cancer include those with uncommon familial syndromes (i.e., hereditary polyposis and hereditary nonpolyposis colorectal cancer [HNPCC]) and persons with longstanding ulcerative colitis.[3,4] Familial syndromes are estimated to account for 6% of all colorectal cancers,[3] and various genetic mutations associated with these syndromes have been identified.[4a] Other principal risk factors include a history of colorectal cancer or adenomas in a first-degree relative, a personal history of large adenomatous polyps or colorectal cancer, and a prior diagnosis of endometrial, ovarian, or breast cancer. In an analysis of two

large cohorts involving over 840,000 patient-years of follow-up, a family history of colorectal cancer was associated with a significant increase in risk in younger persons (1.7–4-fold increase between ages 40 and 60), but was not associated with a significantly increased risk in persons after age 60;[4b] risk was higher in persons with more than one affected relative. The absolute increase in lifetime risk in persons with a family history was modest, however: an estimated cumulative incidence of colorectal cancer by age 65 of 4% vs. 3% in persons without a family history.[4b] Diets high in fat or low in fiber may also increase the risk of colorectal cancer.[3]

Accuracy of Screening Tests

The principal screening tests for detecting colorectal cancer in asymptomatic persons are the digital rectal examination, FOBT, and sigmoidoscopy. Less frequently mentioned screening tests include barium enema and colonoscopy, which have been advocated primarily for high-risk groups. The digital rectal examination is of limited value as a screening test for colorectal cancer. The examining finger, which is only 7–8 cm long, has limited access even to the rectal mucosa, which is 11 cm in length. A negative digital rectal examination provides little reassurance that the patient is free of colorectal cancer because fewer than 10% of colorectal cancers can be palpated by the examining finger.[3]

A second screening maneuver is FOBT. The reported sensitivity and specificity of FOBT for detecting colorectal cancer in asymptomatic persons are 26–92% and 90–99%, respectively (usually based on two samples from three different stool specimens), with the widely varying estimates reflecting differences in study designs.[5–10] Positive reactions on guaiac impregnated cards, the most common form of testing, can signal the presence of bleeding from premalignant adenomas and early-stage colorectal cancers. The guaiac test can also produce false-positive results, however. The ingestion of foods containing peroxidases,[11] and gastric irritants such as salicylates and other antiinflammatory agents,[12] can produce false-positive test results for neoplasia. Nonneoplastic conditions, such as hemorrhoids, diverticulosis, and peptic ulcers, can also cause gastrointestinal bleeding. FOBT can also miss small adenomas and colorectal malignancies that bleed intermittently or not at all.[13,14] Other causes of false-negative results include heterogeneous distribution of blood in feces,[15] ascorbic acid and other antioxidants that interfere with test reagents,[16] and extended delay before testing stool samples.[17]

As a result, when FOBT is performed on asymptomatic persons, the majority of positive reactions are falsely positive for neoplasia. The reported positive predictive value among asymptomatic persons over age 50 is only about 2–11% for carcinoma and 20–30% for adenomas.[6,5,9,18–20] As-

suming a false-positive rate of 1–4%, a person who receives annual FOBT from age 50 to age 75 has an estimated 45% probability of receiving a false-positive result.[21] This large proportion of false-positive results is an important concern because of the discomfort, cost, and occasional complications associated with follow-up diagnostic tests, such as barium enema and colonoscopy.[22,23] Rehydration of stored slides can improve sensitivity, but this occurs at the expense of specificity.[24] In one study, rehydration improved sensitivity from 81% to 92%, but it decreased specificity from 98% to 90% and lowered positive predictive value from 6% to 2%. Due to the high false-positive rate, about one third of the entire screened population of asymptomatic patients underwent colonoscopy for abnormal FOBT results within a 13-year period.[5]

Other tests have been proposed to improve the accuracy of screening for fecal occult blood. Current evidence is equivocal as to whether Hemo-Quant (SmithKline Diagnostics, Sunnyvale, CA), a quantitative measurement of hemoglobin in the stool, has better sensitivity or specificity than does qualitative FOBT.[9,10,25–29] Recently developed hemoglobin immunoassays offer the promise of improved sensitivity and specificity but require further evaluation before being considered for routine screening.[30,31]

The third screening test for colorectal cancer is sigmoidoscopy. Sigmoidoscopic screening in asymptomatic persons detects 1–4 cancers per 1,000 examinations.[32,33] However, the sensitivity and diagnostic yield of sigmoidoscopy screening varies with the type of instrument: the rigid (25 cm) sigmoidoscope, the short (35 cm) flexible fiberoptic sigmoidoscope, or the long (60 cm) flexible fiberoptic sigmoidoscope. Since only 30% of colorectal cancers occur in the distal 20 cm of bowel, and less than half occur in or distal to the sigmoid colon,[34–37] the length of the sigmoidoscope has a direct effect on case detection. The rigid sigmoidoscope, which has an average depth of insertion of about 20 cm[38–44] and allows examination to just above the rectosigmoid junction,[45] can detect only about 25–30% of colorectal cancers. The 35-cm flexible sigmoidoscope, however, can visualize about 50–75% of the sigmoid colon and can detect about 50–55% of polyps. Longer 60-cm instruments have an average depth of insertion of 40–50 cm, reaching the proximal end of the sigmoid colon in 80% of examinations[46,47] with the capability of detecting 65–75% of polyps and 40–65% of colorectal cancers[48–52] Researchers have examined the feasibility of introducing a 105-cm flexible sigmoidoscope in the family practice setting,[53] but it is unclear whether the added length substantially increases the rate of detection of premalignant or malignant lesions. Barium enema studies have confirmed that some neoplasms within reach of the sigmoidoscope may not be seen on endoscopy.[54]

Sigmoidoscopy can also produce false-positive results, primarily by detecting polyps that are unlikely to become malignant during the patient's

lifetime. Autopsy studies have shown that 10–33% of older adults have colonic polyps at death,[55] but only 2–3% have colorectal cancer.[56–58] Depending on the type of adenomatous polyp, an estimated 5–40% eventually become malignant,[59] a process that takes an average of 10–15 years.[60,61] It follows that the majority of asymptomatic persons with colonic polyps discovered on routine sigmoidoscopic examination will not develop clinically significant malignancy during their lifetime. For these persons, interventions that typically follow such a discovery (i.e., biopsy, polypectomy, frequent colonoscopy), procedures that are costly, anxiety provoking, and potentially harmful, are unlikely to be of significant clinical benefit.

Other potential screening tests for colorectal cancer include colonoscopy and barium enema, which appear to have comparable accuracy. About 95% of colorectal cancers are within reach of the colonoscope, and the examination has an estimated 75–95% sensitivity in detecting lesions within its reach.[20,21] Colonoscopy, which requires sedation and often involves the use of a hospital suite, is more expensive than other screening tests and has a higher risk of anesthetic and procedural complications. The estimated sensitivity and specificity of air-contrast barium enema in detecting lesions within its reach are about 80–95% and 90%, respectively, using subsequent diagnosis as a reference standard.[21] Some retrospective studies have reported a higher sensitivity of barium enema for detecting colorectal cancer (about 90–96%),[62,63] with pathologic diagnosis as the reference standard, but these estimates generally do not account for the selection bias introduced by the case-selection methods.

Effectiveness of Early Detection

Persons with early-stage colorectal cancer at the time of diagnosis appear to have longer survival than do persons with advanced disease.[2] Since there is little information on the extent to which lead-time and length biases (see Chapter ii) account for these differences, researchers in the U.S. and Europe launched large clinical trials in the late 1970s to collect prospective data on the effects of screening on co-lorectal cancer mortality.

Two of these trials[5,6] examined the effect of routine FOBT on colorectal cancer mortality. A randomized controlled trial involving over 46,000 volunteers over age 50 found that the 13-year cumulative mortality from colorectal cancer was 33% lower among persons advised to undergo annual FOBT (5.9 deaths per 1,000) than among a control group that was not offered screening (8.8 deaths per 1,000).[5] The report provided insufficient data, however, to determine to what extent observed differences in outcome were attributable to FOBT or to the large number of colonoscopies that were performed due to frequent false-positive FOBT. An analysis of the study data by other authors suggested that one third to one

half of the mortality reduction was due to "chance" selection of persons for colonoscopy,[64] but the assumptions in the analysis have been disputed by the authors.[65] Another controlled trial,[6] which was not randomized, assigned over 21,000 patients to a control group that received a standard periodic health examination or to a study group that was also offered FOBT; both groups received sigmoidoscopy screening. Among new patients (first visit to the preventive medicine clinic), colorectal cancer mortality was 43% lower in the study group than in controls, a difference of borderline statistical significance ($p = 0.053$, one-tail), and there was no difference in outcomes among patients seen previously at the clinic. Recent case-control studies have also reported a 31–57% reduction in risk among persons receiving FOBT.[66,67] Three large clinical trials of FOBT screening, currently under way in Europe, are expected to report their results in the coming years.[7,68,69]

Recent case-control studies have provided important information on the effectiveness of sigmoidoscopy screening. The largest study found that 9% of persons who died of colorectal cancer occurring within 20 cm of the anus had previously undergone a rigid sigmoidoscopic examination, whereas 24% of persons in the control group had received the test.[70] The adjusted odds ratio of 0.41 (95% confidence interval, 0.25–0.69) suggested that sigmoidoscopy screening reduced the risk of death by 59% for cancers within reach of the sigmoidoscope. The investigators noted that the adjusted odds ratio for patients who died of more proximal colon cancers was 0.96. This finding added support to the hypothesis that the reduced risk of death from cancers within reach of the rigid sigmoidoscope was due to screening rather than to confounding factors. Another case-control study reported that the odds ratio for dying of colorectal cancer was 0.21 in screened subjects, and the benefit appeared to be limited to cancers within the reach of the sigmoidoscope.[71]

Older evidence of the effectiveness of sigmoidoscopy screening suffered from important design limitations. A randomized controlled trial of multiphasic health examinations, which included rigid sigmoidoscopy, reported that the study group had significantly lower incidence and mortality rates from colorectal cancer.[72–74] A subsequent analysis of the data, however, revealed that the proportion of subjects receiving sigmoidoscopy and the rate of detection or removal of polyps were similar in both the study and control groups, thus suggesting little benefit from sigmoidoscopy.[75] Two large screening programs found that persons receiving periodic rigid sigmoidoscopy had less advanced disease and better survival from colon cancer than was typical of the general population.[76–78] However, both studies lacked internal controls and used nonrandomized methods to select participants; other methodologic problems with these investigations are outlined in other reviews.[75,79]

An important consideration in assessing the effectiveness of sigmoidoscopic screening is the potential iatrogenic risk associated with the procedure. Complications from sigmoidoscopy are relatively rare in asymptomatic persons but can be potentially serious. Perforations are reported to occur in approximately 1 of 1,000–10,000 rigid sigmoidoscopic examinations.[20,21,32,80] Although there are fewer data available on flexible sigmoidoscopy, the complication rate appears to be less than or equal to that observed for rigid sigmoidoscopy. The reported risk of perforation from colonoscopy is about one in 500–3,000 examinations,[5,81] and the risk of serious bleeding is 1 in 1,000.[5] The estimated risk of perforation during barium enema is 1 in 5,000–10,000 examinations.[82]

There is little useful evidence regarding the effectiveness of colonoscopy or barium enema screening in asymptomatic persons. Several recent studies describe colonoscopy screening of asymptomatic persons, but they report only the anatomic distribution of polyps and do not address clinical outcomes.[48,49,83] A prospective study demonstrated a significantly lower incidence of subsequent colorectal cancer in patients with previously diagnosed adenomas who received periodic colonoscopy and polypectomy, but potential biases in the control groups (historical controls and population incidence rates) prevent definitive conclusions.[84] No studies have directly examined the effectiveness of routine barium enema screening in decreasing colorectal cancer mortality in asymptomatic persons. Modeling studies suggest its effectiveness might be comparable to a screening strategy of periodic sigmoidoscopy.[21]

There is limited information on the optimal age to begin or end screening and the frequency with which it should be performed. The age groups in which screening has been shown to decrease mortality are ages 50–80 for FOBT[5] and over age 45 for sigmoidoscopy.[70] Theoretically, the potential yield from screening should increase beyond age 50 since the incidence of colorectal cancer after this age doubles every 7 years.[2] Modeling studies suggest that beginning screening at age 40 rather than at age 50 offers no improvement in life expectancy.[21] There is little evidence from which to determine the proper age for discontinuing screening. The optimal interval for screening is less certain for sigmoidoscopy than for FOBT, for which there is good evidence of benefit from annual screening. A modeling study of sigmoidoscopy screening estimated that an interval of 10 years would preserve 90% of the effectiveness of annual screening; this model assumes that adenomatous polyps take 10–14 years to become invasive cancers.[21] Another model suggested that an interval of 2–4 years would allow detection of 95% of all polyps greater than 13 mm in diameter.[85] In a case-control study, the risk reduction associated with sigmoidoscopy screening did not diminish during the first 9–10 years after sigmoidoscopy.[70] Other studies suggest that a single sigmoidoscopic

screening examination may be adequate for low-risk individuals,[86] an approach being investigated in the United Kingdom.[87]

Primary preventive measures to prevent colorectal cancer are currently under investigation. An association between colorectal cancer and dietary intake of fat and fiber has been demonstrated in a series of epidemiologic studies (see Chapter 56). Case-control and cohort studies also suggest that aspirin use may decrease the risk of colon cancer.[88–90]

Recommendations of Other Groups

The American Cancer Society recommends annual digital rectal examination for all adults beginning at age 40, annual FOBT beginning at age 50, and sigmoidoscopy every 3–5 years beginning at age 50.[91] Similar recommendations have been issued by the American Gastroenterological Association,[92] the American Society for Gastrointestinal Endoscopy,[92] and the American College of Obstetricians and Gynecologists.[93] The American College of Physicians' (ACP) guidelines, revised in 1995, recommend offering a variety of screening options to persons from age 50 to 70, depending on local resources and patient preferences: flexible sigmoidoscopy, colonoscopy, or air-contrast barium enema, repeated at 10-year intervals. The ACP recommends that annual FOBT be offered to persons who decline these screening tests, but concluded that there was relatively little benefit of continuing endoscopic screening beyond age 70 in individuals who had been adequately screened up to that age.[21] The American College of Radiology recommends screening with barium enema every 3–5 years as an equivalent alternative to periodic sigmoidoscopy.[94] The recommendations of the American Academy of Family Physicians are currently under review.[95] Most organizations recommend more intensive screening of those in high-risk groups (e.g., familial polyposis, inflammatory bowel disease) with periodic colonoscopy or barium enema. The Canadian Task Force on the Periodic Health Examination concluded that there was insufficient evidence to support screening of asymptomatic individuals over age 40 but that persons with a history of cancer family syndrome should be screened with colonoscopy.[96] An expert panel convened by the Agency for Health Care Policy and Research is expected to issue guidelines for colorectal cancer screening and surveillance in 1996.

Discussion

In summary, recent studies have provided compelling evidence of the effectiveness of FOBT and sigmoidoscopy screening, but the evidence is not definitive. At least one randomized controlled trial and several observational studies have shown that annual FOBT in persons over age 50 can reduce colorectal cancer mortality. This evidence does not, however, clarify

whether the observed benefits were due to FOBT or to the effect of performing colonoscopy on a large proportion of the screened population. For sigmoidoscopy, a case-control study supports a strong association between regular screening and reduced colorectal cancer mortality from cancers within reach of the sigmoidoscope. This study was limited, however, by its small number of cases, potential selection biases, and inability to provide prospective evidence of benefit. There are additional concerns about the adverse effects, costs, and optimal frequency of screening. Studies that will help resolve these uncertainties are currently in progress; the final results of ongoing European FOBT trials will be unavailable for several years, however, and a large United States study[97] of FOBT and sigmoidoscopy screening will not be completed until the turn of the century.

An important limitation to the effectiveness of screening for colorectal cancer is the ability of patients and clinicians to comply with testing. Patients may not comply with FOBT for a variety of reasons,[68,98] but compliance rates are generally higher than for sigmoidoscopy. Recent clinical trials report compliance rates of 50–80% for FOBT among volunteers,[5–7,68,69] but lower rates (about 15–30%) have been reported in community screening programs.[99–101] Although the introduction of flexible fiberoptic instruments has made sigmoidoscopy more acceptable to patients,[102] the procedure remains uncomfortable, embarrassing, and expensive, and therefore many patients may be reluctant to agree to this test. A survey of patients over age 50 found that only 13% wanted to receive a sigmoidoscopy examination after being advised that they should receive the test; the most common reasons cited for declining the test were cost (31%), discomfort (12%), and fear (9%).[103] In a study in which sigmoidoscopy was recommended repeatedly, only 31% of participants consented to the procedure,[72–74] but this study was performed during years when rigid sigmoidoscopy was common. Compliance rates as low as 6–12% have been reported. Studies suggest that physician motivation is a major determinant of patient compliance,[104,105] and physicians may be reluctant to perform screening sigmoidoscopy on asymptomatic persons. It has been estimated that a typical family physician with 3,000 active patients (one third aged 50 or older) would have to perform five sigmoidoscopies daily to initially screen the population and two daily procedures for subsequent screening.[33] In addition, examinations using 60-cm sigmoidoscopes are more time-consuming[35–39] and require more extensive training[106–108] than do those using shorter instruments.

Another limitation to screening is its cost. Although a formal cost-effectiveness analysis of screening for colorectal cancer is beyond the scope of this chapter, the economic implications associated with the widespread performance of FOBT and sigmoidoscopy are clearly significant. A single flexible sigmoidoscopic examination costs between $100 and $200.[22,109] A policy

of routine FOBT and sigmoidoscopic screening of all persons in the United States over age 50 (about 63 million persons) would cost over $1 billion per year in direct charges.[109] Others have calculated that FOBT screening alone could cost the United States and Canada between $500 million and $1.2 billion each year.[110,111] Another model predicted that performing annual FOBT on persons over age 65 would cost about $35,000 per year of life saved; adding flexible sigmoidoscopy would increase the cost to about $42,000 to $45,000 per year of life saved.[112] Mathematical models suggest that barium enema screening every 3–5 years might have comparable or superior cost-effectiveness when compared with sigmoidoscopy screening, but neither the clinical effectiveness nor acceptability of barium enema screening has been demonstrated directly in clinical studies.

The downstream effects of screening are also of concern. The logistical difficulties and costs of performing FOBT and sigmoidoscopy on a large proportion of the U.S. population are significant, due to the limited acceptability of the tests and the expense of performing screening and follow-up on a large proportion of the population. Moreover, the tests have potential adverse effects that must be considered, such as false-positive results that lead to expensive and potentially harmful diagnostic procedures. Studies that have reported reduced mortality from FOBT used rehydrated slides to increase sensitivity, thereby producing a higher proportion of false-positive results than with nonrehydrated slides; 32% of the annually screened population underwent colonoscopy during a 13-year follow-up period.[65] If this rate is extrapolated to the 63 million Americans over age 50 who would receive annual FOBT, it can be predicted that about 20 million persons would require colonoscopy.

The full implications of this "screening cascade" need to be considered, along with the scientific evidence of clinical benefits, before reaching conclusions about appropriate public policy. For example, using nonrehydrated slides rather than rehydrated slides could substantially reduce the adverse effects and costs of a national screening program. As noted earlier, data from a major screening trial suggest that using nonrehydrated slides rather than rehydrated slides could increase the positive predictive value of FOBT from 2% to 6%, subjecting far fewer screened persons to unnecessary colonoscopy. This improvement in specificity, however, comes at the expense of sensitivity, which decreased from 92% with rehydration to 81% in nonrehydrated slides. The use of nonrehydrated slides would therefore allow a much larger proportion of persons with cancer to escape detection.

The special considerations that apply to persons at increased risk of colorectal cancer are complicated by inadequate epidemiologic and effectiveness data and inconsistent disease classifications. Having a single family member with colorectal cancer does not carry the high risk associated with hereditary cancer syndromes (e.g., familial polyposis, HNPCC).[4,113] A fam-

ily history that is suggestive of the latter includes a pattern of diagnoses consistent with autosomal dominant inheritance of a highly penetrant disorder. Characteristic features include a family history of colorectal cancer being diagnosed at an early age, frequent cases of multiple primary cancers, or florid adenomatous colonic polyps. Performing periodic colonoscopy to screen for cancer in these groups may be justified in light of the high risk of disease and the incidence of proximal colonic lesions, but there is no direct evidence to determine the optimal strategy in this population.

CLINICAL INTERVENTION

Screening for colorectal cancer is recommended for all persons aged 50 or over ("B" recommendation). Effective methods include FOBT and sigmoidoscopy. There is insufficient evidence to determine which of these screening methods is preferable or whether the combination of FOBT and sigmoidoscopy produces greater benefits than either test alone. Although there is good evidence to support FOBT on an annual basis, there is insufficient evidence to recommend a periodicity for sigmoidoscopy screening. A frequency of every 3–5 years has been recommended by other groups on the basis of expert opinion, and a well-designed case-control study suggests that protection remains unchanged for at least 10 years after rigid sigmoidoscopy. Current evidence suggests that at least some of the benefits of FOBT in reducing colorectal cancer mortality may be achieved through colonoscopic evaluation of abnormal results. Widespread FOBT or sigmoidoscopy screening is therefore likely to generate substantial direct and indirect costs. Appropriate public policy may require consideration of factors other than the scientific evidence of clinical benefit. The appropriate age to discontinue screening has not been determined.

Patients who are offered these tests should receive information about the potential benefits and harms of the procedures, the probability of false-positive results, and the nature of the tests that will be performed if an abnormality is detected. FOBT screening should adhere to current guidelines for dietary restrictions, sample collection, and storage. Although slide rehydration increases the sensitivity of FOBT, it also decreases specificity, and there is insufficient evidence to determine whether rehydration results in better outcomes than screening with nonrehydrated slides. Sigmoidoscopy should be performed by a trained examiner. The instrument should be selected on the basis of examiner expertise and patient comfort. Longer (e.g., 60-cm instrument) flexible sigmoidoscopes have greater sensitivity and are more comfortable than shorter, rigid sigmoidoscopes.

There is insufficient evidence to recommend for or against routine screening with digital rectal examination, barium enema, or colonoscopy

("C" recommendation). Recommendations against using these tests for screening average-risk persons may be made on other grounds (e.g., availability of alternate tests of proven effectiveness, inaccuracy of digital rectal examination, costs and risks of colonoscopy).

In persons with a single first-degree relative with colon cancer, it is not clear that the modest increase in the absolute risk of cancer justifies routine use of colonoscopy over other screening methods. The increased risk of developing cancer at younger ages may justify beginning screening before age 50 in persons with a positive family history, however, especially when affected relatives developed colorectal cancer at younger ages. Direct evidence of the benefit of screening in younger persons is not available for any group. For persons with a family history of hereditary syndromes associated with a very high risk of colon cancer (i.e., familial polyposis or HNPCC), as well as those previously diagnosed with ulcerative colitis, high-risk adenomatous polyps, or colon cancer, regular endoscopic screening is part of routine diagnosis and management; referral to specialists is appropriate for these high-risk patients.

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