Systematic Evidence Review
Number 7

Screening for Colorectal Cancer in Adults

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Systematic Evidence Review
Number 7

Screening for Colorectal Cancer In Adults

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
Rockville, MD 20852
http://www.ahrq.gov

Contract No. 290-97-0011
Task Order No. 3
Technical Support of the U.S. Preventive Services Task Force

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AHRQ Publication No. 02-S003
July, 2002

Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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* The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

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Acknowledgments
This study was developed by the RTI-UNC Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (Contract No. 290-97-0011), Rockville, MD. We acknowledge the assistance of Jacqueline Besteman, JD, MA, EPC Program Officer; David Atkins, MD, MPH, Chief Medical Officer, Center for Practice and Technology Assessment, AHRQ; and Dana Best, MD, MPH, the AHRQ Task Order Officer. We extend our appreciation as well to RTI-UNC EPC staff, including Russell Harris, MD, MPH, co-director of the EPC's Clinical Prevention Center; Sonya Sutton, BSPH, Sheila White, and Loraine Monroe of Research Triangle Institute; and Mark Dowell and Carol Krasnov of the University of North Carolina at Chapel Hill Cecil R. Sheps Center for Health Services Research. Finally, we thank the external peer reviewers of the draft of this review: Robert Smith, MD, American Cancer Society, Atlanta, GA; Jerome B. Simon, MD, Hotel Dieu Hospital, Kingston, Ontario, Canada; Sidney Winawer, MD, Memorial Sloan-Kettering Cancer Center, New York, NY; Ann G. Zauber, Ph.D., Memorial Sloan-Kettering Cancer Center, New York, NY; Mary F. Mitchell, American College of Obstetricians and Gynecologists, Washington, DC; Ralph J. Anderson, MD, American College of Obstetricians and Gynecologists, Washington, DC; Vincenza Snow, MD, American College of Physicians/American Society of Internal Medicine, Boston, MA; Robert Fletcher, MD, Harvard Pilgrim Health Care, Boston, MA; Joe Selby, MD, MPH, Kaiser Permanente, Oakland, CA; and Robin McLeod, MD, Canadian Task Force on Preventive Care, Toronto, Ontario, Canada.

Structured Abstract

Context: Colorectal cancer is an important cause of cancer-related morbidity and mortality in the United States. Screening has the potential to reduce the morbidity and mortality from colorectal cancer through early detection and removal of early-stage cancers or precancerous adenomatous polyps.

Objective: We conducted a systematic review for the US Preventive Services Task Force to assess the effectiveness and cost-effectiveness of different colorectal cancer screening tests.

Data sources: We used recently conducted systematic reviews, the second edition of the *Guide to Clinical Preventive Services*, the British National Health Service Economic Evaluation database, and focused searches of MEDLINE from 1966 through September 2000 to identify relevant studies for inclusion. We also conducted hand-searches, review of bibliographies, and consultations with context experts to assure completeness.

Study selection: When available, we included the most recent high-quality systematic review and then supplemented that review with a search for more recent articles. Full MEDLINE searches were performed to examine the accuracy of double-contrast barium enema, the rates of complications for each of the available screening tests, and for studies of the cost-effectiveness of screening. Two reviewers examined the results of each of the full searches and determined by consensus which articles should be abstracted into evidence tables.

Data extraction: One reviewer abstracted the information from the final set of studies into evidence tables, and a second reviewer checked them for accuracy.

Data synthesis: Direct evidence from multiple well-conducted randomized trials supports the effectiveness of fecal occult blood testing (FOBT) in decreasing colon cancer incidence and reducing mortality from colorectal cancer compared with no screening for average-risk adults over age 50. Data from well-conducted case-control studies support the effectiveness of sigmoidoscopy and possibly colonoscopy in reducing colon cancer mortality as well. A nonrandomized trial and indirect evidence support the use of combination FOBT and sigmoidoscopy. Indirect evidence from diagnostic accuracy studies suggests that double-contrast barium enema or virtual colonoscopy may also be effective compared with no screening. Data are insufficient to determine with confidence and precision the most effective or cost-effective strategies or the age at which screening should be stopped.

Conclusions: Colorectal cancer screening is effective in reducing mortality from colorectal cancer. Current data are insufficient to determine the most effective or cost-effective strategy for screening, although all major strategies have favorable cost-effectiveness ratios compared with no screening.

Chapter 1. Introduction

Burden of Suffering and Epidemiology

Colorectal cancer is the fourth most common form of cancer in the United States and has the second highest mortality rate, accounting for about 130,000 new cases and about 56,000 deaths in the year 2000.[1] The incidence of colorectal cancer is low until ages 45 to 50 years; it then rises throughout the remainder of a person's lifetime. Mortality from colorectal cancer begins to rise about 10 years after incidence rises. Men are slightly more likely to develop colorectal cancer than women, but the risk is high enough for both men and women potentially to benefit from screening; African-Americans are more likely to die from colorectal cancer than caucasians. Figure 1 shows the incidence and mortality of colorectal cancer by age and gender.[2] A 50-year-old person has about a 5% lifetime risk of being diagnosed with colorectal cancer and a 2.5% chance of dying from it.[3] Currently, 35% to 40% of patients diagnosed with colorectal cancer are detected when the cancer is localized; 35% to 40% have regional spread; and 20% to 25% have distant metastases.[2] Estimated 5-year survival is greater than 90% in persons with Dukes' Stage A cancers, 80% for Dukes' Stage B, 65% in persons with regional spread (Dukes' C), and 8% in those with Stage D cancers (distant metastases). The average patient dying of colorectal cancer loses 13 years of life.[1]

Polyps and Cancer – There are two types of polyps: hyperplastic and adenomatous. Hyperplastic polyps do not become cancers and require no further attention here. Some adenomatous polyps develop into cancer but most will not. The prevalence of adenomatous polyps at age 50 is 20% to 25%; this level increases to 50% by ages 75 to 80.[3] Limited data suggest that less than 1% of small adenomatous polyps (smaller than 1 cm in size) will eventually develop into cancer. Of large polyps (larger than 1 cm in size), about 10% will become malignant within 10 years and about 25% after 20 years.[4] Our current understanding of the biology of colorectal neoplasia suggests that most (more than 80%) of colorectal cancers arise from precancerous adenomatous polyps ("adenomas").

Risk Factors for Colorectal Cancer

More than 60% of colorectal cancers occur in persons at average risk. Table 1 shows the relative risk of colorectal cancer for persons with certain characteristics. Approximately 20% of colorectal cancer cases occur among patients with a family history of colorectal cancer in a first-degree relative.[5] In an analysis of 2 large cohorts involving more than 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- to 4-fold increase between ages 40 and 60) but not with a significantly increased risk for persons older than age 60; risk was higher in persons with more than 1 affected relative.[6] Six percent of colon cancers occur among persons with uncommon hereditary syndromes (e.g., familial adenomatous polyposis [FAP] or hereditary nonpolyposis colorectal cancer [HNPCC]) that confer a high risk of colorectal cancer. Persons with longstanding ulcerative colitis are at increased risk, as are persons with a history of large adenomatous polyps or colorectal cancer.[3,7] Adenomatous polyps diagnosed in a first-degree relative before age 60 increases the risk of colorectal cancer (relative risk [RR]=1.78; 95% confidence interval [CI] 1.18 — 2.67).[8] A prior diagnosis of endometrial or ovarian cancer also conveys increased risk,

particularly for cancers occurring below age 50; a history of breast cancer increases risk only slightly, if at all.[9-11, 12,12,13,13]

The relationship between diet and colon cancer has been the subject of extensive epidemiologic research. Numerous observational studies have examined whether certain dietary elements are associated with an increased or decreased incidence of colon cancer or adenomatous polyps.[14] Diets low in fat and red meat, and high in fiber and fruits and vegetables, have been associated with lower risks of colorectal cancer, but no evidence shows that changes in diet affect the subsequent rate of new cancers. High levels of physical activity are also associated with lower rates of colorectal cancers but, again, it is unclear if this relationship is causal or if it is confounded by other factors.[15] A full examination of the observational evidence regarding the relationship between dietary functions or physical activity and colorectal cancer is beyond the scope of this paper.

Prior Task Force Recommendations

In 1996 the USPSTF recommended screening for colorectal cancer with fecal occult blood testing (FOBT), sigmoidoscopy, or both tests.[16] The USPSTF did not recommend for or against other means of screening (digital rectal examination [DRE], barium enema, colonoscopy) on the grounds that evidence was insufficient. They also recommended that FOBT be performed yearly but did not specify an interval for sigmoidoscopy.

To update the 1996 review and provide the scientific evidence for the USPSTF to make new recommendations, we undertook a systematic review of screening for colorectal cancer in average-risk adults. Related questions, such as screening of higher-risk patients, surveillance of patients with previous polyps or cancers, or diagnosis of patients with colon-related symptoms, are mentioned briefly but were not reviewed for this report.

Chapter 2. Methods

We document here the procedures that the Research Triangle Institute - University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) used to develop this systematic review on screening for colorectal cancer.[17] We describe development of the analytic framework and key questions, management of the literature search and synthesis, and conduct of the external peer review process. During these steps, EPC staff collaborated with two members of the USPSTF who acted as liaisons for this topic; they are co-authors of this review. The interactions took place chiefly by electronic mail and telephone conference calls. Steps in the development of this review were presented at USPSTF meetings in December 2000 and March 2001, when EPC staff and USPSTF members were able to discuss the analytic framework, key questions, and final draft findings and conclusions.

Analytic Framework and Key Questions

The USPSTF examined the following overarching key question related to colorectal cancer screening: What are the benefits and adverse effects of screening average-risk adults over the age of 50 for colorectal cancer with office FOBT (oFOBT) and DRE, home FOBT, sigmoidoscopy, FOBT and sigmoidoscopy together, double contrast barium enema (DCBE), colonoscopy, or computed tomography (CT) colography? Each major testing strategy was examined separately, yielding seven subsidiary key questions.

To guide the review process, the authors developed the analytic framework depicted in Figure 2. The framework begins with asymptomatic adults ages 50 and older with no special risk factors for colorectal cancer. Screening of high-risk patients is addressed separately. Average-risk adults can undergo one of several strategies for screening. The screening strategies involve 1 or more tests that are repeated at some interval. Harms, including complications of the screening test, false positives, and economic costs, can arise at the screening phase. Persons screening negative are retested after some interval of time.

Persons screening positive by any method other than screening colonoscopy then undergo diagnostic colonoscopy. If the colonoscopy is negative for adenomas and cancers, screening can be suspended for at least 5 years. If the colonoscopy identifies neoplasms, they are biopsied. Adenomatous polyps usually can be removed during the initial colonoscopy. If cancer is detected, the patient receives further diagnostic studies to assess the stage of disease and then receives treatment (usually surgery, with radiotherapy or chemotherapy as adjuvant therapy in some circumstances). Harms can again arise at the time of colonoscopy or from treatment. Detection and removal of adenomas can prevent future cancers. Early detection and treatment of early-stage cancers can reduce colorectal cancer mortality.

Literature Searching and Analysis

We used the second edition of the *Guide to Clinical Preventive Services,* existing systematic reviews, focused MEDLINE literature searches from 1966 through September 2000, review of the British National Health Service Economic Evaluation database, and hand-searches of key articles to identify the literature relevant to our key question. For those questions for which we performed MEDLINE searches, 1 reviewer examined the abstracts of the articles identified in the initial search to determine relevancy. A second reviewer examined the excluded articles and

differences were resolved by consensus. Two reviewers examined the full text of the remaining articles to determine final eligibility.

We then abstracted the final set of eligible articles and created evidence tables. When systematic reviews were considered for inclusion, two investigators examined each review to assure that it followed methods similar to those used in our searches.

Peer Review Process

A draft version of this report underwent review by several content experts and stakeholders (see acknowledgements). Based on their comments and those of the USPSTF members, the report was revised.

Chapter 3. Results

Our main question concerns the evidence about the benefits and adverse effects of different colorectal cancer screening strategies for average-risk adults. The available screening tests for colorectal cancer are the DRE (with or without a single office-based FOBT), home FOBT, sigmoidoscopy, DCBE, colonoscopy, and CT colography. Each of these approaches, as well as the combination of FOBT and sigmoidoscopy, has been considered as a means of screening for colorectal cancer. Other combinations of tests have not been well evaluated and are not discussed here.

We review here the evidence about the accuracy and effectiveness of the above screening strategies for average-risk adults. When available, we focus on evidence from trials or observational studies that have measured patient outcomes, particularly changes in colorectal cancer mortality. When such data are not available, we present indirect information, such as screening test accuracy. For each modality, we also report the adverse effects or harms associated with its use and its acceptability to patients. In each case, we attempt to consider the entire screening pathway, rather than just the initial test itself.

Digital Rectal Examination and Office Fecal Occult Blood Testing

Although DRE with a single office-based FOBT is commonly performed by practitioners, the effectiveness of this approach in reducing colorectal cancer mortality has not been studied directly in a clinical trial or observational study. Evaluation of its effectiveness can be based only on indirect information, mostly regarding test accuracy.

DRE — The sensitivity of a screening DRE is low: less than 10% of colorectal cancers arise within reach of the examining finger.[3] Some of these lesions will be symptomatic and thus the sensitivity of DRE in asymptomatic adults over 50 with colorectal cancer is likely to be even lower. The specificity of a positive DRE has not been examined in average-risk outpatients.

A case-control study from Northern California Kaiser Permanente examined the effect of screening DRE on mortality from colorectal cancer.[18] The investigators identified Kaiser patients ages 45 and older who died of distal rectal cancers between 1971 and 1986 and selected matched controls from their patient membership. They examined medical records to determine if cases and controls had undergone screening DREs within a year of diagnosis and found no difference between groups after controlling for potential confounders (adjusted odds ratio, 0.96; 95% CI, 0.56 - 1.7). Checking longer periods of time before diagnosis did not change the results. Their findings did not support a relationship between DRE and risk reduction of death from distal rectal cancers, although the confidence interval was wide and did not exclude an important protective effect.

Office FOBT — The value of a single office-based FOBT obtained at the time of the DRE is also based on indirect evidence. Theoretically, oFOBT should be less sensitive than the traditional 3-sample home-performed FOBT because only 1 sample is taken. In addition, the failure to allow the degradation of vegetable peroxidases that sometimes produce false-positive results and the potential trauma from the examination itself have been proposed as reasons that the oFOBT may also be less specific (able to produce a negative result when no colorectal cancer is present) than a properly performed home FOBT.

Published studies of FOBT have shown that the yield of the 3-sample card strategy is higher than that for the first sample card alone. Yamamoto and Nakama found that the first test card

detected 58% of cancers found in a large study of FOBT in Japan.[19] The second card increased the yield to 89% and the final card to 100%. Almost half (42%) of the cancers detected would have been missed by using only the first card.

Two studies have compared retrospectively the specificity of oFOBT and home FOBT. Bini et al. examined the records for 672 patients who were referred for colonoscopy because of a positive FOBT.[19] The positive predictive values (PPV) for cancer were similar in each group (11.7% for oFOBT; 11.3% for home FOBT). Sensitivity could not be evaluated. Although the study attempted to exclude patients with abdominal signs and symptoms, the nonrandomized nature of the comparison made it difficult to determine if the 2 groups (those receiving oFOBT and those receiving home FOBT) had an equal risk for colorectal cancer. If the risks were different, then these results cannot be interpreted as demonstrating equivalent specificity.

Eisner and Lewis performed a similar study among 270 patients with positive FOBT (144 obtained on oFOBT from a DRE, 126 on home FOBT) referred for colonoscopy.[20] The 2 groups had a similar frequency of colonic abnormalities. However, patients with positive oFOBT on DRE were mostly inpatients (77%), whereas those with positive results obtained on home FOBT were not (17%). This finding suggests that the groups were not comparable, making conclusions about test specificity unreliable.

Fecal Occult Blood Testing

General Description — The home FOBT requires the patient to collect and submit 3 stool test cards (each card with 2 separate stool samples from each of 3 consecutive bowel movements). The intervals that have been studied are every 1 or 2 years. Because laboratory data have shown that certain dietary substances can cause inaccurate test results, patients are generally asked to restrict their diet for 3 days before and during sample collection. The cards are then returned for processing.

A positive home-FOBT result (1 or more test windows positive) requires a diagnostic examination with colonoscopy. If a positive FOBT is followed by a negative colonoscopy, FOB testing can be suspended for at least 5 years. A negative FOBT is repeated in 1 to 2 years, depending on the choice of test interval.

A process called rehydration, in which distilled water is added to the slides just before the test reagents are applied, is sometimes used to increase sensitivity of the FOBT. The increase in sensitivity, however, comes at the cost of decreased specificity.[21]

Accuracy — Determining the sensitivity and specificity of rehydrated or unrehydrated FOBT is methodologically difficult. Traditional definitions of sensitivity and specificity are based on evaluations of tests at a single point in time. Measuring the performance of a screening program entails multiple tests performed over time for each participant. Because studies of longitudinal screening have not performed a criterion standard examination (such as colonoscopy) after each test iteration, data on single-test sensitivity cannot be derived directly from the existing longitudinal trials, although methods exist to estimate it.[22] Studies that have measured the sensitivity and specificity of a single iteration of FOBT among truly asymptomatic subjects have found a sensitivity for an unrehydrated test to be approximately 40%; its specificity appears to be 96% to 98%. Rehydration increases sensitivity to 60% but lowers specificity to 90%.[21,23,23] Because the pretest probability for cancer is low, the majority of positive FOBT are false positives. The reported PPV for unrehydrated slides among asymptomatic persons over age 50 is 5% to 18% for any cancer and 20% to 40% for the combination of curable cancer or large

adenomas.[21] The PPV in the large, randomized Minnesota screening trial (described below) was only 2.2 %, using mostly rehydrated slides. The PPV for cancer and large polyps varied depending on how many of the 6 test windows were positive. When only 1 was positive, the PPV was 0.9%; for 4 positives, it was 1.9%; and for 6 positives, it was 4.5%. The PPVs for adenomas more than 1 cm in size were 6.0%, 7.5%, and 7.9%, respectively.[24,25]

For longitudinal programs of screening, potentially more relevant global measures of test accuracy are the proportion of cancers identified by screening (the longitudinal analogue of single-test sensitivity) and the proportion of patients requiring a criterion standard examination but not diagnosed with cancer (the longitudinal analogue of the false-positive rate or 1 minus specificity). In the annual screening arm of the 13-year Minnesota trial, which used primarily rehydrated test cards and had a high initial rate of participation (about 90%), 49% of patients who developed colorectal cancer were identified through screening; 38% of all patients had had at least 1 colonoscopy. With biennial testing, 39% of cancers were detected by screening and 28% required colonoscopy. In the European trials in the United Kingdom and Denmark, which were population based and 8 to 10 years in duration, researchers used biennial testing and had lower rates of participation (60% to 70% completed first screen), 27% of cancers were detected by screening (49% of cancers occurring in participants); only 5% of patients underwent colonoscopy.[24,26,27]

Eddy developed a model of colorectal cancer screening that projected that a patient undergoing annual unrehydrated FOBT from age 50 to age 75 has an estimated 45% probability of receiving a false-positive result.[28] Long-term data are not available to validate this estimate.

Other stool tests have been proposed to improve the accuracy of screening for fecal occult blood. Although some newer techniques, including quantitative measures of heme and genetic stool markers, hold promise, they have not been evaluated with respect to mortality reduction (as the Hemoccult™ FOBT has been).[21,29 29]

Effectiveness — The effectiveness of FOBT for reducing colorectal cancer mortality has been examined directly in 3 randomized controlled trials. All trials used the Hemoccult™ test kit. Among these 3 trials, risk of death from colorectal cancer was decreased by 15% to 33% (Table 2). The two trials with smaller reductions in mortality (15% and 18%) were conducted in Europe (the United Kingdom and Denmark), randomized patients prior to agreement to participate and thus had lower participation rates, used biennial screening, and did not perform rehydration.

The third trial, conducted in Minnesota, randomized volunteers, used annual and biennial testing, and rehydrated most test cards (83%). Cumulative mortality from colorectal cancer was 33% lower among persons randomized 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). In the original report of the Minnesota trial, those assigned to biennial screening did not show a reduction in mortality; however, a recent report after 18 years of follow-up showed that a significant 21% reduction in mortality difference had emerged.[30] Another recent report from the 18-year follow-up of the Minnesota trial showed that the incidence of colorectal cancer was decreased by 20% and 17% for the annual and biennial groups, respectively, compared with controls.[25]

A fourth trial conducted in Sweden has not reported mortality results. However, previously unpublished data described in the systematic review by Towler et al. suggests that the Swedish investigators did not find a significant mortality reduction after 2 rounds of rehydrated testing (RR = 0.88; 95% CI, 0.69 - 1.12).[31]

Adverse Effects — FOB testing itself has few adverse effects, but false-positive FOBTs lead to further tests, such as colonoscopy, during which adverse effects may occur. The specific adverse effects of colonoscopy are described below. Theoretically, a previously negative FOBT could falsely reassure patients and lead to delayed response to the development of colorectal symptoms if a cancer were to develop, but this concern has not been evaluated empirically.

Acceptability — Some patients report that they find the FOBT unpleasant or difficult to perform. Nevertheless, initial rates of FOBT completion when the test is ordered by the patient's provider have been reported to be 50% to 70% and can be increased by an average of 14% with the use of a reminder system.[32,33] The rates of long-term adherence have not been well studied except in the randomized trials of screening. In those trials, about 50% of participants completed all tests in the series; 80% of initial acceptors completed the second test in the series.[32] When offered the choice of FOBT alone, sigmoidoscopy alone, or both tests together, 36% to 53% of subjects in one clinic-based study preferred FOBT alone, depending on the amount of information provided and the imposition of co-payments for sigmoidoscopy.[34]

Sigmoidoscopy

General Description — Sigmoidoscopic screening today is performed with a 60 cm flexible endoscope. The test, also referred to as flexible sigmoidoscopy or "flex sig," is generally recommended every 5 years, though no empiric data testing different intervals are available. To prepare for the test, patients are usually asked to take 2 enemas the morning of the examination. No sedation is used. If a screening examination detects cancer, large adenomatous polyps (greater than 1 cm), sessile polyps, or carcinoma *in situ*, a colonoscopy is then performed. If no polyps are found, the sigmoidoscopy is repeated in 5 years.

The question of which findings on sigmoidoscopy should trigger immediate colonoscopy is a matter of ongoing debate. Some researchers advocate performing colonoscopy when any polyp is detected; others have recommended performing colonoscopy only after detection of large, multiple, or high-risk adenomas. Recent data suggest, however, that although finding large or high-risk adenomas in the distal colon increases the chance that high-risk proximal adenomas are also present, the finding of small adenomas or hyperplastic polyps also increases that chance somewhat. The decision about when to perform colonoscopy requires a decision about what chance of missing an important proximal finding is acceptable.[35,36]

Accuracy — First-time sigmoidoscopic screening in asymptomatic persons detects about 7 cancers and 60 large or high-risk adenomas per 1,000 examinations.[37] The 60-cm instrument has an average depth of insertion of 40 to 50 cm. It will reach the proximal end of the sigmoid colon in 80% of examinations.[38] Because the sigmoidoscope can examine only the distal portion of the colon, important proximal lesions may not be identified. The actual proportion of patients who will have an important proximal lesion missed, however, will include only those patients who do not have any distal lesions that would trigger colonoscopy.

Two recent studies have examined the question of what proportion of patients with cancer or advanced adenomas will be missed with sigmoidoscopy, stratifying their results on the basis of different potential rules for which findings on sigmoidoscopy trigger full colonoscopic examinations.[35,36] Lieberman et al. conducted such a study among 3,121 patients in the Department of Veterans Affairs system.[35] They found that 80% of the 329 patients with advanced adenomas (defined as adenomas that were over 1 cm in size, multiple, or had villous features) had at least one adenoma (of any size) in the distal colon, defined as distal to the

splenic flexure. If the distal colon were defined as only the rectum and sigmoid, this figure fell to 68%. The type of distal adenoma was associated with the likelihood of an advanced proximal lesion, but the finding of no distal lesion did not rule out the possibility of a proximal lesion. Imperiale et al. conducted a similar study among 1994 adults ages 50 and older, who were taking part in a workplace screening program.[36] Overall, 104 patients had advanced neoplasms, defined as those lesions larger than 1 cm or having villous features, high-grade dysplasia, or carcinoma *in situ*. Overall, sigmoidoscopy would have detected 81 of the 104 patients with advanced lesions (78%). Assuming patients with an advanced distal finding all would under colonoscopy. Sigmoidoscopy can also produce false-positive results, by detecting either hyperplastic polyps that do not have malignant potential or adenomatous polyps that are unlikely to become malignant during the patient's lifetime. Studies of diagnostic accuracy cannot measure whether adenomas (small or large) identified and removed would have gone on to become cancers, so investigators have not typically counted them as false positives. This decision means that evaluation and comparison with other methods such as FOBT are difficult.

Effectiveness — Thiis-Evensen et al performed a small randomized trial of sigmoidoscopy screening in Norway.[39] In 1983, they randomized 799 men and women ages 50-59 drawn from a population registry to be offered screening flexible sigmoidoscopy (400 patients) or to be controls (399 patients). Intervention patients were contacted and asked to participate in screening; control patients were not contacted until the study's conclusion in 1996. All patients with polyps on sigmoidoscopy underwent immediate diagnostic colonoscopy and had surveillance examinations 2 and 6 years later. All study participants (intervention and control) were offered endoscopic testing in 1996.

Of the 400 intervention patients, 324 (81%) agreed to have sigmoidoscopy in 1983. Approximately 34 percent (34.6%) were found to have at least one polyp, (defined as any circumscribed, elevated lesion) and 1 person was found to have cancer on the initial examination. Over the 13-year course of the trial, 2 colorectal cancers were diagnosed in the intervention group and 10 in the control group (RR for colorectal cancer incidence = 0.2; 95% CI, 0.03 - 0.95). One person who was assigned to the intervention group, but who never had a screening examination, died from colorectal cancer; 3 deaths occurred in the control group (RR = 0.50; 95% CI, 0.10 - 2.72). Overall mortality was higher in the intervention group than in the control group (14% vs. 9%; RR=1.57; 95% CI, 1.03 - 2.40), mostly because of an excess of cardiovascular deaths. There was no clear relationship between the excess deaths and any complications from the procedures. The authors reported only 1 complication (water intoxication from an excessive preparation regimen) in 788 colonoscopic examinations, 432 sigmoidoscopic examinations, and 1,734 polypectomies.

These data suggest that sigmoidoscopic screening with colonoscopic follow-up for any positive finding may be effective in reducing the incidence of future colorectal cancer. They also suggest the possibility of a reduction in mortality from colorectal cancer, although the study was too small to estimate precisely the magnitude of benefit.

Two ongoing trials using flexible sigmoidoscopy can be expected to report their initial results within 5 years. One trial is examining the effect of once-in-a-lifetime sigmoidoscopy in the United Kingdom;[37] a second trial in the United States is examining sigmoidoscopy every 5 years with the assumption that patients are receiving FOBT as well.[40]

Well-designed case-control studies have provided important information on the effectiveness of sigmoidoscopy screening. Selby et al. examined data from Northern California Kaiser Permanente and 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 who did not die of a cancer within 20 cm of the anus had received the test.[41] The adjusted odds ratio of 0.41 (95% CI, 0.25-0.69) suggested that sigmoidoscopy screening reduced the risk of death by 59% for cancers within reach of the rigid 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 could be attributed to screening rather than to confounding factors. The risk reduction associated with sigmoidoscopy screening did not diminish during the first 9 to 10 years after the test was performed.[41] Although the Selby et al. study mostly used rigid sigmoidoscopes, in another case-control study supporting the effectiveness of sigmoidoscopy, 75% of the examinations were performed with a flexible instrument.[42]

Adverse Effects — Estimates of bowel perforations from sigmoidoscopy have generally been in the range of 1 to 2 per 10,000 examinations or lower, particularly since the introduction of the flexible sigmoidoscope.[43] Atkin et al. recently reported initial results from their sigmoidoscopy screening trial.[37] Experienced endoscopists performed sigmoidoscopy in 1,235 asymptomatic adults ages 55 to 64 years; 288 patients had polyps removed during the examination. Adverse effects, including pain, anxiety, or any degree of bleeding, were assessed by a written questionnaire immediately after the test and by a postal questionnaire 3 months later. Of all subjects, 3.2% (40/1,235) reported bleeding (16/288 or 5.5% after polypectomy; 24/947 or 2.5% of only diagnostic studies); 1 patient required admission; none required a transfusion. Of all subjects, 14% reported moderate pain and 0.4% reported severe pain. More than 25% of patients reported gas or flatus. No perforations were reported, but 1 patient died from peritonitis after a complicated open surgical procedure to remove a severely dysplastic adenoma. A recent study of endoscopic complications from the Mayo Clinic in Arizona identified 2 perforations during sigmoidoscopy out of 49,501 procedures.[44]

Acceptability — Studies examining the acceptability of sigmoidoscopy to patients have reached mixed results, depending on the setting and whether the evaluation was prospective or retrospective. Studies conducted in primary care settings have found rates of adherence of 25% to 50% for the initial test, but data are insufficient to predict the proportion of patients who will continue to complete subsequent examinations in a program of screening. [32] When given information about screening options and offered the choice of FOBT alone, sigmoidoscopy alone, or both tests together, most patients in an academic internal medicine clinic preferred both tests or FOBT alone; only 8% to 13% preferred sigmoidoscopy alone, suggesting that patients willing to undergo sigmoidoscopy usually are also interested in FOBT. [34]
Verne et al., compared the acceptability of FOBT alone, flexible sigmoidoscopy alone, or the combination of the 2 tests in a randomized controlled trial.[45] They identified 3,933 patients ages 50 to 75 years from the registry of a general practice in Great Britain. One of the investigators, a practitioner in the clinic, excluded 5% of the patients as ineligible because they had died, moved away, been diagnosed previously with colorectal cancer, or had been recently screened. Potentially eligible subjects were randomized to receive by mail an invitation to FOBT, sigmoidoscopy, or both tests. Those invited to do FOBT received the Hemoccult™ cards in the mail; those invited to do sigmoidoscopy were sent an appointment and the preparatory material. Those randomized to be offered both tests were asked to do the FOBT first.

Subjects assigned to sigmoidoscopy alone were more likely to complete their test than subjects assigned to FOBT (47% vs. 32%). Subjects offered both tests completed them both

30% of the time. More subjects in the combined group completed sigmoidoscopy than FOBT (38% vs. 32%).[45,46]

FOBT and Sigmoidoscopy

General Description — The strategy of combining FOBT every year and sigmoidoscopy every 5 years involves many of the same issues that are described for each test individually. If either test is positive, colonoscopy is performed. Therefore, in a year in which both tests are due, it is prudent to perform FOBT first, so that if it is positive, colonoscopy can be performed instead of sigmoidoscopy.

Effectiveness — Currently no randomized trials with colorectal cancer mortality as an endpoint compare the performance of FOBT alone or sigmoidoscopy alone against a strategy of performing both tests.

Winawer et al. conducted a nonrandomized study of more than 12,000 first-time attendees at a preventive health clinic in New York.[47] Participants were assigned to 1 of 2 groups. The control group received a rigid sigmoidoscopy examination at the first visit and was invited to return for annual re-checks. Intervention patients received the rigid examination and were also asked to complete Hemoccult™ FOBT cards. Patients with adenomas more than 3 mm on sigmoidoscopy or a positive FOBT underwent full colonic examination with barium enema and colonoscopy. Few subjects continued to participate after the first examination (20% had FOBT at year 2 and 15% at year 3). Incidence of colorectal cancer and mortality were assessed over a 9-year period; follow-up data were available for 97% of subjects.

Demographic and clinical data suggest that the groups were comparable, despite the absence of randomization. More colorectal cancers were detected on initial examination among intervention patients than control patients (4.5 vs. 2.5 per 1,000 participants). Incidence rates (cancers detected after the initial examination) were similar between groups (0.9 per 1,000 person-years in each group). Colorectal cancer mortality was 0.36 per 1,000 patient years in the intervention group and 0.63 per 1,000 patient-years among controls ($p = 0.11$).

Thus, adding FOBT to rigid sigmoidoscopy appears to increase the yield of initial screening and may reduce mortality. Because rigid sigmoidoscopy is no longer used for screening, the generalizability of these results to the use of FOBT plus flexible sigmoidoscopy is unclear. It is also unclear if the incremental yield of combined screening will change after additional rounds of testing.

Accuracy — Recent randomized trials from Europe have examined the additional diagnostic yield from performing sigmoidoscopy in addition to FOBT at one point in time for patients who were not part of an ongoing screening program.

Berry et al. randomized patients in the UK to receive an invitation for FOBT alone or an invitation for FOBT followed by an invitation for flexible sigmoidoscopy.[48] They examined the rate of acceptance of the tests and the yield for "significant neoplasia" (cancers or large polyps). Subjects had a mean age of 61 and slightly more than half were women.

The investigators found that about 50% of subjects in each group accepted and completed FOBT. Of those accepting FOBT in the combined testing arm, 20% also accepted sigmoidoscopy. In the FOBT only group, 6 significant lesions were detected (4 large polyps, 2 cancers) a yield of 2/1000 patients randomized. In the combined group, 7 patients had significant lesions based on FOBT (6 had large polyps, 1 had cancer). The addition of sigmoidoscopy identified 20 additional patients with large polyps and 2 additional patients with cancers, a yield of 8.9/1000

patients randomized. Therefore, the additional yield of important lesions was 6.9 per 1,000 patients randomized for combined testing, despite the low uptake of sigmoidoscopy. Among patients completing their tests, the yield for the combined strategy was 44.2 per 1,000 compared with 4.2 per 1,000 in the FOBT-only group.

Rasmussen et al. performed a similar trial in Denmark.[49] They randomized almost 11,000 residents of Funen, Denmark, to be offered either a single FOBT or a FOBT and a flexible sigmoidoscopy. Among those randomized to FOBT alone, 56% completed the test. In the FOBT-plus-sigmoidoscopy group, 40% completed both tests, 2% completed one of the assigned tests but not the other, and 58% did not complete any test. In the FOBT-only group, 73 subjects had a positive test (2.4% positive rate); 4 patients were found to have cancer, 14 had large polyps, 7 had small polyps, and 48 were false positives. In the combined testing group, 488 of 2,222 subjects (22%) had a positive test, defined as a positive FOBT or the finding of any polyp larger than 3 mm or cancer on sigmoidoscopy. Of the 488 positives, 12 had cancer, 72 had large polyps, 181 had small polyps, and 223 were false positives. Many of the neoplasms were detected only by sigmoidoscopy (5 of 12 cancers, 60 of 72 large polyps, 175 of 181 small polyps); no cancers and only 1 large polyp were detected by a positive FOBT when the sigmoidoscopy was negative.

The investigators also used cancer registry data to examine the effect of screening on colorectal cancer incidence 2 to 5 years after the tests were performed. The total numbers of cancers diagnosed in each group were equal, but more cancers in the FOBT-only group were detected clinically rather than by screening (18 of 22 for FOBT only versus 8 of 20 for those assigned to both tests, $p = 0.01$). Cancers detected clinically were more advanced in stage than those detected by screening, but the trial was not powered sufficiently to examine the effect on mortality.

Verne et al. used data from a general practice in Great Britain to examine the yield of 1 round of screening for patients assigned to FOBT alone, flexible sigmoidoscopy alone, or both tests together.[45] All persons with a positive FOBT underwent colonoscopy. Persons with large polyps on sigmoidoscopy underwent colonoscopy as well. Persons with polyps less than 5 mm detected in the rectum on sigmoidoscopy were biopsied: those with hyperplastic polyps did not undergo colonoscopy, but those with adenomas did.

Seven patients had a positive FOBT: 1 had a Duke's Stage C cancer, 1 had a large (2 cm) adenoma; 1 a single 2 mm adenoma; and 1 had 2 small adenomas. The 3 other patients had no findings. What proportion also had positive sigmoidoscopies was not clear.

Among the 401 subjects who completed both tests, 31 had adenomas on sigmoidoscopy (all less than 1 cm) and 1 had a Stage A cancer. This cancer and 30 of the 31 polyps were negative on FOBT. These findings suggest that adding sigmoidoscopy significantly increases the yield over FOBT alone. The data are insufficient to determine the additional yield of adding FOBT to sigmoidsocopy alone.[45]

Thus, the combination of FOBT and sigmoidoscopy apparently has a greater yield for significant neoplasia (cancers and large polyps) than does FOBT alone. According to data from the 3 European trials, adding FOBT does not seem to increase the yield obtained with sigmoidoscopy alone, after one round of testing.[45,47,49-51] Winawer et al., however, did find an increased yield from adding FOBT to rigid sigmoidoscopy and also showed a mortality reduction that was of borderline statistical significance; the data are limited because the compliance was very low for subsequent rounds of testing.[47] The incremental yield of combined testing after the first round may be different, but its impact has not been fully evaluated.

Adverse Effects — The adverse effects for the combined strategy of FOBT and sigmoidoscopy are the sum of the adverse effects of each test alone.

Acceptability — The acceptability of doing both FOBT and flexible sigmoidoscopy is affected by the downsides and effort of both tests. Nevertheless, data from an academic internal medicine clinic suggest that more than one-third of informed patients prefer to have both tests rather than either one alone.[34] Verne et al. found that adherence to combined testing was lower than that for sigmoidoscopy alone or FOBT alone (signoidoscopy alone 47%, FOBT alone 32%, both tests 30%).[45] The acceptability of both tests compared with colonoscopy or barium enema has not been evaluated.

Double Contrast Barium Enema

General Description — The double contrast barium enema (DCBE) is a radiologic test in which barium and air are instilled in the colon and x-rays are made in various positions. Patients usually prepare for the test with a laxative the night before the examination, a clear liquid diet, and 1 or 2 enemas the morning of the test. The examination itself takes 20 to 40 minutes. No sedation is used. If the test is positive, a colonoscopy is performed; if it is negative, it is repeated in 5 years.

Accuracy — We identified 12 studies from our literature search that met our criteria for inclusion in the analysis of the accuracy of DCBE in the diagnosis of colorectal cancer or adenomatous polyps.[50-61]

Many of the studies of DCBE accuracy were performed in patients with known disease; some of these patients had originally been diagnosed because of a positive DCBE and thus may overestimate accuracy. Others have looked retrospectively at patients with known disease to determine whether a barium enema had been performed within some period before diagnosis. In these studies, the sensitivity can be distorted depending on the time interval before diagnosis that is examined for "false negative" DCBE examinations. In addition, these patients (who had DCBE for some indication) may differ systematically from screening patients.

In general, these studies have found sensitivity levels of 80% to 90% for cancer, but these data cannot be extrapolated to screening with confidence. Bloomfield, in his prospective study from Australia, examined the sensitivity and specificity of DCBE for colorectal cancer and polyps;[54] he found that sensitivity was 86% and specificity was greater than 95% when detection of either a polyp or cancer was considered to be a positive finding.

The ideal study for measuring the accuracy of DCBE would examine test performance among a sample of asymptomatic patients undergoing screening. Each patient would have a DCBE examination, followed by a colonoscopy performed by an examiner masked to the result of the barium enema. In the event that lesions identified on DCBE were not seen on colonoscopy, a repeat unmasked colonoscopic examination would be performed immediately after the first colonoscopy to determine if a lesion was truly present. Results would be reported separately for large adenomatous polyps and cancer. Such a study has not been performed to date; sensitivity and yield will likely be higher on the first examination than they will on subsequent examinations of patients who initially test negative.

The National Polyp Study is a randomized trial of different intervals of surveillance (examinations at 1 and 3 years vs 3 years only) after polypectomy. In this study, Winawer et al. measured the accuracy of DCBE as compared with colonoscopy, using the technique of comparing DCBE with masked and then unmasked colonoscopy.[62] A total of 580 patients (74%

men, 61% over age 60) who had been diagnosed with adenomatous polyps had 1 or more paired examinations 1, 3, or 6 years after initial detection and removal of polyps. The paired examination consisted first of a colonoscopy performed by an endoscopist masked to the DCBE result; after the first test, any lesions identified on DCBE that had not been detected on the first colonoscopy were then looked for again on a second examination. The sensitivity of DCBE (compared to colonoscopy) for polyps less than 0.5 cm was 32% (95% CI, 25%-39%); for polyps 0.6 to 1 cm, it was 53% (95% CI, 40% -66%); for polyps larger than 1 cm, including 2 cancers, it was 48% (95% CI, 24%-67%). Of 470 examinations in which no polyps were identified on colonoscopy, barium enema was positive in 83 (specificity 85%).

The Winawer et al. study examined patients who recently had had colonoscopy and removal of all polyps. Their results, therefore, may have limited generalizability for screening, because screening is a situation in which most subjects will not have had a recent colonoscopic examination and polypectomy and hence may be more likely to have large polyps or cancers. However, the low sensitivity for large polyps found in this study is of concern and may limit the effectiveness of screening with DCBE.

Effectiveness — No trial has examined the ability of screening barium enema to reduce the incidence or mortality from colorectal cancer.

Adverse Effects — The estimated risk of perforation during barium enema is low. In the study from Kewenter and Brevinge, no perforations or other complications occurred among the 1,987 screening patients undergoing barium enema as part of their screening work-up.[63] Blakeborough et al. surveyed UK radiologists about the complications of barium enema during a 3-year period from 1992 through 1994.[64] All examinations were included, whether they were performed for patients who were acutely ill or not. Important complications of any type occurred in 1 in 10,000 examinations. Perforation occurred in 1 of 25,000 examinations; death occurred in 1 in 55,000 examinations, although whether such deaths resulted from the procedure is not clear.

Acceptability — Patients' acceptance of barium enema screening has not been evaluated. Studies examining the relative discomfort of barium enema and colonoscopy have produced inconsistent results. [65,66]

Colonoscopy

General Description — Colonoscopy has not been widely used as a screening test, although several centers have been testing its feasibility and accuracy.[35] No testing interval has been examined empirically, though testing every 10 years is the most commonly considered strategy. Some experts have advocated a once-in-a-lifetime examination between 55 and 65 years of age.[13]

The bowel cleansing preparation can be difficult. It may require that patients drink several liters of nonabsorbable laxative the night before the test or use a powerful laxative. The test itself is performed with conscious sedation and lasts 20 to 40 minutes. Patients need to have someone accompany them to the examination and drive them home. They are unable to return to work the same day, and some may miss a second day of work.[67]

Colonoscopy allows the biopsy and removal of polyps at the time of the screening examination itself. If cancer is detected, further assessment and treatment can be pursued. If the test is negative, it is repeated at 10 years.

Accuracy — The accuracy of colonoscopic screening is difficult to evaluate because colonoscopy is commonly used as the criterion standard exam, making the calculation of

sensitivity difficult. One method of evaluating sensitivity, tandem colonoscopic examinations, has found that the sensitivity is 90% for large adenomas and 75% for small adenomas (less than 1 cm); sensitivity for cancer is likely to be greater than 90%.[68]

The recent identification of flat lesions that can be missed on regular colonoscopy suggests that some histologic variants do not pass through the same process of detectability as is proposed in the typical adenoma-carcinoma sequence.[69] If flat lesions account for 10% of all adenomas, sensitivity of all endoscopic screening may be lower than previously thought.

The specificity of colonoscopy with biopsy is generally reported to be 99% or 100%, but this assumes that all adenomas that are detected represent "true positives." For all forms of screening, most adenomas that are detected, especially small adenomas, will never develop into cancer. If detection of an adenoma that will not become cancer is considered a false positive that subjects a patient to risk without benefit (see complications below), then the actual "specificity" is much lower.

Effectiveness — The ability of colonoscopy to prevent colorectal cancer cases or mortality has not been measured in a screening trial. The National Polyp Study estimated that 76% to 90% of cancers could be prevented by regular colonoscopic surveillance examinations, based on comparison with historic controls.[62] However, these results should be interpreted with caution, because the comparison groups were not from the same underlying population, which could introduce bias. In addition, the participants in the trial all had had polyps detected and removed, which limits their generalizability to the average screening population.

Muller and Sonnenberg, in a case-control study at VA hospitals, found that patients diagnosed with colorectal cancer were less likely to have had previous endoscopic procedures: the odds ratio for colon cancer was 0.51 (95% CI, 0.44-0.58) and for rectal cancer, 0.55 (95% CI, 0.47-0.64).[70] When colonoscopy was considered alone, the odds ratios were 0.47 (95% CI, 0.37-0.58) and 0.61 (95% CI, 0.48-0.77), respectively.

The reduction in colorectal cancer incidence and mortality from prevention and early detection with screening colonoscopy every 10 years has been estimated in recent colorectal cancer screening models to be 58% (incidence reduction) and 61% (mortality reduction).[71]

Adverse Effects and Costs — Colonoscopy, which requires sedation and skilled support personnel, is more expensive than other screening tests and has a higher risk of procedural complications, particularly when polypectomy is performed. The use of conscious sedation adds the risk of complications attributable to the anesthetic.

We conducted a systematic review of studies examining the principal complications of colonoscopy. We focused on hemorrhage and perforation but noted the less frequent complications of death, infections, sedation-related events, and chemical colitis as well. We identified 19 articles that examined complications of colonoscopy (see Table 3).[35,36,43,44,67,72-85]

Two recent studies examined the incidence of complications from colonoscopy performed in screening populations.[35,36] One study was conducted among patients in Veterans' Affairs medical centers and another among employees of a large corporation using experienced, highly skilled endoscopists. In the VA study by Lieberman et al, 10 of 3121 patients (0.3%) had major complications during or immediately following the procedure, including 6 who had bleeding requiring hospitalization and 1 each with a stroke, myocardial infarction, Fournier's gangrene, and thrombophlebitis.[35] Three other patients died within one month, though the authors did not believe the deaths to be related to the procedure. In the study by Imperiale et al, 1994 patients ages 50 and older underwent colonoscopy.[36] One (0.05%) had a perforation that did not require

surgery and 3 (0.15%) had bleeding that required emergency room visits but not admission or surgery. There were no deaths.

Apart from these 2 screening studies, most of the studies we identified were retrospective reviews of endoscopy records from US university hospitals. Publication dates ranged from 1982 to 2000 for reviews of data between 1972 and 1997. Two studies used prospective data questionnaires to assess complications more fully.[67,73]

Fewer than half of the studies distinguished between diagnostic and therapeutic procedures (those in which a polypectomy was performed). The proportion of patients undergoing screening, follow-up, or surveillance examinations versus procedures for symptomatic processes varied among the studies included; moreover, this information was not reported for several studies, making extrapolation to screening difficult.

The rates of perforation for diagnostic procedures were low, ranging from 0.029% to 0.61%. Most studies did not give the rate of post-colonoscopy bleeding following diagnostic procedures. In 1 prospective study of 250 patients undergoing diagnostic procedures no bleeding events and no perforations had occurred after 24 hour follow-up.[67] The complication rates for therapeutic procedures were higher: 0.07% to 0.72% for perforations and 0.2% to 2.67% for bleeding. Deaths occurred infrequently and were more likely to occur in symptomatic patients with acute problems or those with comorbid conditions. The death rates reported ranged from 0.0037% to 0.06%. The mortality rate for screening may be on the lower end of this range; 1 cost-effectiveness analysis estimated it as 1 per 20,000 patients.[23] Other clinically relevant complications were identified too infrequently and measured too inconsistently to estimate accurately their true incidence.

The limited number of screening studies and reliance upon information extracted from the written record or databases in the majority of other studies limit the quality of the data and their ability to accurately inform estimates of possible adverse effects from colonoscopy screening. Publication bias may also affect the accuracy of our estimates, because centers with better rates of complications may be more likely to publish their data. In addition, reports that present only an overall complication rate that mixes diagnostic and therapeutic procedures are less helpful, because the single (combined) rate probably overstates the complication rate for diagnostic procedures and underestimates it for therapeutic procedures.

Acceptability — One study has examined informed patient preferences for colonoscopy compared with other methods of screening in a population of patients that had considerable previous screening experience. The investigators found that a plurality (38%) preferred colonoscopy.[86]

Computed Tomography Colography

General Description — CT colography, also known as "virtual colonoscopy," has recently begun to be considered as a means of screening for colorectal cancer. The examination currently requires a preparation similar to colonoscopy, followed by installation of air through a rectal tube. CT scan images are then made of the colon, and a computer reconstructs them into virtual images of the colonic lumen. The test can be performed in 10 to 15 minutes. If the test is positive, the patient will need to undergo colonoscopy. If negative, they will presumably be rescreened after some interval.

Effectiveness — No studies have evaluated the effectiveness of CT colography in reducing morbidity or mortality from colorectal cancer.

Accuracy — Several studies conducted in research settings among highly skilled radiologists have evaluated the accuracy of CT colography compared with that of colonoscopy.[87,88] Initially reported sensitivity and specificity values for cancers and large polyps were in the range of 85% to 90%, but recent reports have suggested lower levels of accuracy for less experienced examiners. Small and flat polyps are less well visualized on CT colography than are cancers and large polyps**.**

Adverse Effects – The data are currently insufficient to measure the frequency of complications with CT colography**.**

Acceptability – The acceptability and feasibility of CT colography have not been examined.

When to Start or Stop Colorectal Cancer Screening

Information on the optimal age to begin or end screening and the frequency with which it should be performed is limited. The age groups in which screening has been shown to decrease mortality are ages 50 to 80 years for FOBT and age 45 and older for sigmoidoscopy.[31,41] Theoretically, the potential yield from screening should increase beyond age 50 because the incidence of colorectal cancer after this age doubles every 7 years.[1] Eddy's cost-effectiveness model suggests that beginning screening at age 40 rather than at age 50 offers less than a 1-day average improvement in life expectancy.[28]

We found no direct evidence to allow determination of the proper age for discontinuing screening. The randomized trials of screening suggest, however, that several years of life expectancy may be required to realize the benefits of screening. The optimal interval for screening is less certain for sigmoidoscopy than for FOBT, for which there is good evidence of benefit from annual and biennial screening, although annual screening appears to be more effective.

Cost and Cost-effectiveness

Several analyses have examined the cost-effectiveness of colorectal cancer screening. Our systematic review of such analyses (to be reported in a separate paper[89]) included studies of the cost-effectiveness of individual screening modalities compared with no screening and those that compared different modes of screening.

We identified 6 high-quality cost-effectiveness analyses. For 5 studies, we used the most recent complete publication.[23,28,71,89-91] [Vijan et al., personal communication] In general, the studies focused on the impact of screening on a cohort of adults ages 50 and older who had been screened at regular intervals from ages 50 to 85 or death. Each analysis considered direct costs; none considered indirect costs such as the cost of the time required to perform screening or treatment. Most used fee schedules of Medicare or other payers to estimate costs. Results were presented as average or incremental cost in dollars per life-year saved. None attempted to quality-adjust the value of the life-years.

Our main analyses (Table 4) show average cost-effectiveness ratio values (costs per life-year saved) for each of the major strategies standardized to year 2000 dollars. Nearly all show cost-effectiveness ratios less than $30,*000* per life-year saved, supporting the finding that, compared with no screening, any reasonable strategy appears to be cost-effective using common US thresholds.

Five teams examined the incremental cost-effectiveness of different strategies.[Vijan et al., personal communication][23,71,90,91] Their conclusions about which test(s) were most effective and least costly varied between analyses and within analyses, depending on assumptions about the biologic behavior of colorectal cancer, adherence, and costs of colonoscopy (Table 5). Of the studies considering each major strategy, some found annual FOBT plus sigmoidoscopy every 5 years to have the best performance; others favored colonoscopy every 10 years. The Sonnenberg et al. analysis favored colonoscopy as well, but it did not evaluate the strategy of FOBT plus sigmoidoscopy.[91]

Screening Patients at Higher than Average Risk of Colorectal Cancer

As noted in the introduction, patients at increased risk of colorectal cancer account for about 30% to 35% of colorectal cancer cases. Considering screening patients at highest risk, such as those with rare hereditary syndromes and inflammatory bowel disease including ulcerative colitis, was beyond the scope of this review; such patients may require special care including genetic counseling. Patients with a family history of colorectal cancer are commonly encountered in primary care. They can be identified by systematic elicitation of family histories as a routine part of preventive care. Little direct evidence, however, guides the initiation, frequency, and intensity of screening for these patients. Guidelines based on expert opinion and information about the natural history of the disease have recommended beginning screening 10 years before the age at which the family member had been diagnosed.[3,8]

Chapter 4. Discussion

Overall Findings of Effectiveness and Cost-Effectiveness

Our systematic review supports the effectiveness of screening as a means of reducing colorectal cancer mortality. Table 6 summarizes the strength of evidence supporting each of the different means of screening for colorectal cancer. For FOBT, 3 high-quality randomized trials have shown disease-specific mortality reductions of 15% to 33% over 8 to 13 years. High-quality case-control studies have shown that sigmoidoscopy and possibly colonoscopy are associated with decreased mortality within the reach of the scope. The combined strategy of FOBT and sigmoidoscopy is supported by 1 nonrandomized trial showing reduction in mortality with the addition of FOBT to rigid sigmoidoscopy [47] and by indirect evidence showing increased yield with both tests compared with FOBT alone.

Although barium enema or virtual colonoscopy have not been studied as extensively as other modalities for screening, some indirect evidence suggests that they may also be effective but further data are required in screening populations. Multiple cost-effectiveness analyses have combined these indirect data and estimated that screening by any of the commonly considered strategies appears to prevent morbidity and mortality with cost-effectiveness ratios that compare favorably with other acceptable preventive strategies, such as mammography in women over age 50.

Although colorectal cancer screening is supported by strong direct and indirect evidence, current data are insufficient to define which strategy is most effective or cost-effective. In the face of good general evidence supporting screening but uncertainty about the most effective method for doing so, providers and patients may benefit from discussing the pros and cons of the different methods and incorporating patients' preferences in the decision about how to screen. Future developments with respect to new screening modalities, better chemoprophylactic agents, and improved understanding of the effects of diet and exercise on disease incidence may change the available options for reducing disease burden in average-risk patients.

Future Research Needs

Several areas of colorectal cancer screening and prevention warrant additional research. First, there is a critical need to learn more about adherence to screening among informed patients. Second, we need better data on the real-world complication rates of colonoscopic screening and polypectomy, including whether complications become more or less likely as volume increases. The accuracy of barium enema, virtual colonoscopy, and genetic stool tests (or other novel noninvasive tests) should be evaluated in screening populations. Some have called for a randomized trial of colonoscopy to determine its actual effectiveness. The cost of such a trial, particularly if colonoscopy were to be compared to other screening modalities rather than to no screening, would be quite high; and many years of follow-up would be required for differences to emerge. Additional data from randomized trials are also needed to help improve understanding of the effectiveness of chemopreventive agents such as nonsteroidal anti-inflammatory drugs, calcium, or estrogen. Behavioral factors, including physical activity, dietary fat, dietary fiber, and fruit and vegetable consumption, appear to be related to colorectal

cancer incidence; further research is needed to determine better if these relationships are causal or are the result of uncontrolled confounding.

Despite its apparent effectiveness, colorectal cancer screening is currently underutilized by age-eligible adults. The multiple reasons for low utilization include patient-, provider-, and system-specific barriers.[32] Effective colon cancer screening requires an ongoing effort. Screening with FOBT, for example, requires offering testing to 1,000 people for 10 years to save 1 life. Although this level of effort may seem inefficient or low yield, the potential benefit is large and the costs per person are small, thus, the cost-effectiveness ratio is very favorable compared with other preventive measures. Several strategies have shown effectiveness in raising screening rates, at least in some settings over the short term. These include reminder systems, patient decision aids, and mass screening efforts through employers or other organizations. Further research is needed to determine whether such systems can maintain their effect over time.

Table 1. Relative Risk of Colorectal Cancer

Risk Factors	Relative Risk (95% CI)
Family history of colorectal cancer in a first-degree relative before age 60[3]	1.7 - 4.0*
Family history of adenomatous polyps in a first-degree relative before age 60[8]	1.8 (1.2, 2.7)
Personal history of breast cancer[9]	1.1 (1.0, 1.2)
Personal history of endometrial cancer [12,13]	
Diagnosis before age 50	3.4 (2.7, 4.2)†
Diagnosis age 50-64	0.93 (1.2, 1.8)
Personal history of ovarian cancer[12,13]	
Diagnosis before age 50	3.7 (2.7, 4.8)
Diagnosis age 50-64	1.5 (1.2, 1.8)

* For patients age 40-60; older patients appear to have lower risk.

† 95% confidence interval CCI.

Table 2. Trials of Fecal Occult Blood Test

Trial Characteristics	Minn*		UK†	Denmark‡
Frequency of testing	**Annual**	**Biennial**	**Biennial**	**Biennial**
Duration of follow-up years	18	18	8	10
Hydration of slides	Yes	Yes	No	No
Requiring colonoscopy, %	38%	28%	5%	5%
Mortality reduction, %	33%	21%	15%	18%

* Minn = Minnesota; Source = Mandel et al., 1999.[30]

† UK = United Kingdom; Source = Hardcastle et al., 1996.[26]

‡ Source = Kronborg et al., 1996.[27]

Table 3. Complications of Colonoscopy

Study	Study Design (inclusive years)	Setting	Total Procedures	Perforation Rate (All)	Bleeding Rate (All)	Total Therapeutic Procedures	Perforation Rate-Therapeutic	Bleeding Rate-Therapeutic	Mortality Rate
Newcomer et al., 1999[67]	Prospective enrollment phone survey 1 week after procedure	Community based multispecialty clinic	250	NR*	NR	0	0	0	0.0000%
Eckardt et al., 1999 [72]	Prospective evaluation of complications (1995-1997)	Referral center	2500	0.08%	0.24%	429	0.23%	1.40%	0.0000%
Zubarik et al., 1999[73]	Prospective	Referral center	1196	NR	2.10%	NR	0	NR	0.0000%
Wexner et al., 1998[74]	Retrospective review	Two centers	2069	0.15%	0.10%	353	0.85%	0.57%	0.0000%
Farley et al., 1997[75]	Retrospective review (1980-1995)	Referral center	57,028	0.08%	NR	NR	NR	NR	NR
Foliente et al. 1996[76]	Retrospective review (1987-1993)	Referral center	6684	0.22%	NR	NR	NR	NR	0.0500%

Table 3. Complications of Colonoscopy (continued)

Study	Study Design (inclusive years)	Setting	Total Procedures	Perforation Rate (All)	Bleeding Rate (All)	Total Therapeutic Procedures	Perforation Rate-Therapeutic	Bleeding Rate-Therapeutic	Mortality Rate
Gibbs et al.,1996 [77]	Retrospective review of post-procedural admissions for hemorrhage (1989-1993)	Referral center	12058	NR	0.11%	NR	NR	NR	NR
Ure et al., 1995[78]	Retrospective review (early 1990s)	NR	656	0	0.61%	195	0	2.10%	0.0000%
Lo and Beaton, 1994[79]	Retrospective review (1986-1992)	Referral center	26,708	0.05%	NR	9519	0.07%	NR	0.0037%
Rosen et al., 1993[80]	Retrospective review of post-procedural admissions for hemorrhage (1987-1991)	Community based hospital	NR	NR	NR	4721	NR	0.42%	NR
DiPrima et al., 1988[81]	Prospective review + 10 day post-procedural f/u	Referral center	302	0.66%	1.66%	138	0.72%	3.60%	0.0000%

Table 3. Complications of Colonoscopy (continued)

Study	Study Design (inclusive years)	Setting	Total Procedures	Perforation Rate (All)	Bleeding Rate (All)	Total Therapeutic Procedures	Perforation Rate-Therapeutic	Bleeding Rate-Therapeutic	Mortality Rate
Nivatvongs, 1988[82]	Retrospective review of all polypectomies (1972-1986)	Referral center	1190	NR	NR	1190	0.59%	0.84%	NR
Brynitz et al., 1986[83]	Retrospective review (1975-1984)	NR	1748	0.63%	0	NR	0.7% (0.2-1.8%)	NR	0.0600%
Webb et al., 1985[84]	Retrospective review (1975-1982)	Referral center	591 (1000 polypectomies)	0	0.80%	1000	0	0.80%	0.0000%
Macrae et al., 1983[85]	Retrospective review (1971-1980)	Referral center	5000	0.12%	0.96%	1795	0.11%	2.67%	0.0600%
Nelson et al., 1982[43]	Retrospective review (1972-1980)	Urban county hospital	1207	0.24%	NR	NR	NR	NR	0.0000%

*NR= Not reported

Table 4. Average Cost-Effectiveness Ratios for Selected Screening Strategies for Colorectal Cancer*

Screening Strategy†	Study and Costs per Life-Year Saved					
	Eddy, 1990[28]	Wagner et al., 1996[23]	Frazier et al., 2000[71]	Khandker et al., 2000[90]	Sonnenberg et al., 2000[91]	Vijan et al.,‡
FOBT q1	**13,432**	16,075	13,656	17,805	**10,463**	**5,691**
FS q5	NS§	**14,141**	**12,804**	**15,630**	39,359	19,068
FOBT + FS	30,775	16,144	18,693	22,518	NS	17,942
DCBE q5	19,563	15,974	25,624	21,712	NS	NS
COL q10	NS	26,243	22,012	21,889	11,840	9,038

* Costs per life-year saved converted to year 2000 dollars. Bold typeface indicates best average cost-effectiveness ratio.

† FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; DCBE = double contrast barium enema; COL = colonoscopy; q1 = every year; q5 = every 5 years; q10 = every 10 years.

‡ Vijan et al., is personal communication of unpublished data.

§ NS = Not studied

Table 5. Preferred Strategy at Different Cost-Effectiveness Levels for Each of the Cost-Effectiveness Analyses

	Preferred Strategy If Willing to Pay:			
Studies	**< $20,000 / LYS***	**$20-30,000 / LYS***	**$30-50,000 / LYS***	**$50-100,000 / LYS***
Wagner et al., 1996[23]	DCBE q5	DCBE q5	FOBT q1 + FS q5	FOBT q1 + FS q5
Wagner, et al., 1996[23].†	COL q10	FOBT q1 + FS q5	FOBT q1 + FS q5	FOBT q1 + FS q5
Frazier et al., 2000[71]	FOBT q1 + FS q5	FOBT q1 + FS q5	FOBT q1 + FS q5	FOBT q1 + FS q5
Khandker et al., 2000.[90]	FS q5	FOBT q1	COL q10	COL q10
Sonnenberg et al., 2000[91]	COL q10	COL q10	COL q10	COL q10
Vijan et al.‡	COL 55/65	COL 55/65	COL 55/65	COL 55/65

* LYS indicates life years saved; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; DCBE = double contrast barium enema; COL = colonoscopy; q1 = every year; q5 = every 5 years; q10 = every 10 years.

† Assumes a 50% sensitivity with barium enema.

‡ Vijan et al., is personal communication of unpublished data; 55/65 indicates colonoscopy performed at age 55 and 65 only.

Table 6. Strength of Evidence about Screening Strategies

Test	Direct?* Evidence	Evidence Level	Internal Validity	External Validity
Fecal occult blood testing	Y	I	G	G
Sigmoidoscopy	Y	II	G	F
Fecal occult blood testing and sigmoidoscopy combined	+/-	II	F	F
Double contrast barium enema	N	III	F	F
Colonoscopy	+/-	II	F	F

*+/- indicates not sure

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Figure 1. Cancers of the Colon and Rectum: Average Annual Age-Specific SEER Incidence per 100,000 Persons and U.S. Mortality Rates By Gender, 1992-1996

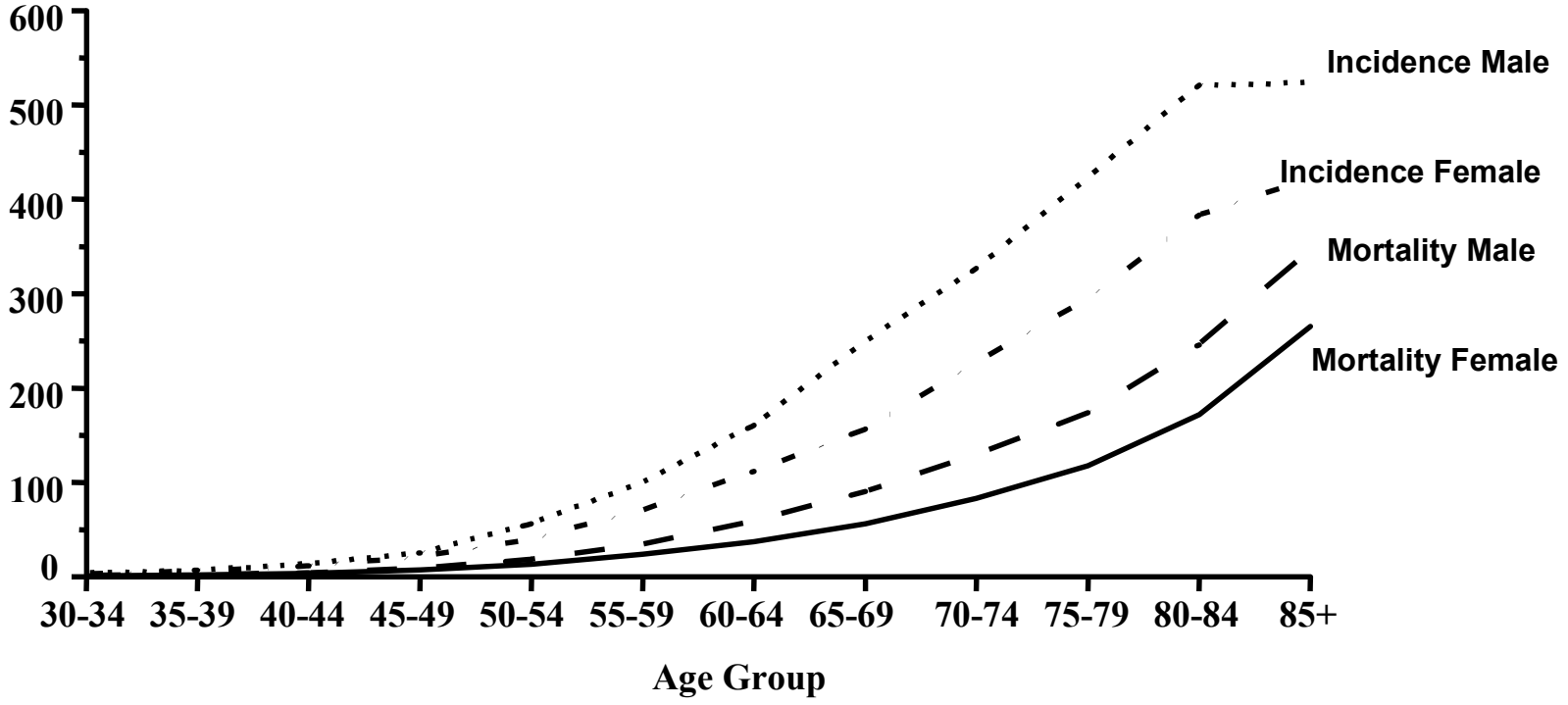

Figure 2. Colorectal Cancer (CRC) Screening: Analytic Framework