Colonoscopy as a Screening Test for Colorectal Cancer in Average-Risk Individuals

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Screening for colorectal cancer has become the standard of care and is currently recommended by most major health organizations, including the American Cancer Society. Randomized controlled trials using fecal occult blood testing as the screening strategy have shown a reduction in mortality due to colorectal cancer. However, colorectal cancer differs from other cancers in that a variety of screening tests have been approved and recommended by experts. The advantages and disadvantages of different screening tests have been the subject of intense debate. Colonoscopy has theoretical advantages over other screening tests, including direct visualization of the entire colon and, more importantly, removal of precancerous adenomatous lesions. This review discusses the advantages and disadvantages of colonoscopy as a screening test for colorectal cancer with regard to efficacy, cost-effectiveness, and patient compliance.


CRC = colorectal cancer; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; QALY = quality-adjusted life-year; RCT = randomized controlled trial

Colorectal cancer (CRC) is the fourth most common cancer and second leading cause of cancer deaths in the United States. About 135,000 new cases were diagnosed in 2001, resulting in approximately 56,000 deaths. Screening efforts have become considerably important in identifying early, curable CRC.

SCREENING AND SURVEILLANCE

Screening involves actively seeking out persons asymptomatic for the disorder in question and asking them to undergo a procedure to identify those at sufficient risk who would benefit from further investigation or direct preventive action. Surveillance is the use of more complex, sometimes invasive tests to diagnose a disease that occurs at a higher frequency in persons having another disease or condition that predisposes them to the disease that is being detected by surveillance, eg, cancer in patients with ulcerative colitis and cancer in patients with Barrett epithelium. Although the terms screening, early detection, mass screening, routine screening, individualized screening, and case finding are used interchangeably, the term individualized screening is best applied to CRC screening activities because physicians normally recommend screening tests to patients in private clinical settings in a 1-to-1 format. An individual with an average risk for CRC has only age as a risk factor. Other risk factors that place a person at increased risk include a family history of CRC (including but not limited to hereditary nonpolyposis colon cancer), adenomatous polyposis coli, personal history of adenomas, CRC, inflammatory bowel disease, and family history of adenomas. However, about 75% of CRCs occur in people without the aforementioned risk factors. For such average-risk individuals, screening for CRC is recommended if they are 50 years of age or older because the incidence of adenomas and subsequently that of CRC increases significantly between 40 and 50 years of age.

Colorectal cancer is a relatively common disease and, if detected at an advanced stage, can be lethal. It has a detectable, curable preclinical stage (adenoma) over a period of approximately 8 to 12 years and advances relatively slowly from early stages (Duke A and B), in which the prognosis is favorable, to advanced stages (Duke C and D), in which the prognosis is more limited. The detection and removal of adenomas and early-stage CRC has been shown to result in increased survival, and various screening tests are available. Thus, CRC is ideally suited for screening.

SCREENING TESTS CURRENTLY RECOMMENDED FOR CRC

Five different screening strategies for CRC have been recommended by the Agency for Healthcare Policy and Research, now known as the Agency for Healthcare Research and Quality, for average-risk individuals. These strategies include annual fecal occult blood test (FOBT), flexible sigmoidoscopy (FS) every 5 years, annual FOBT with FS every 5 years, double-contrast barium enema every 5 to 10 years, and colonoscopy every 10 years. The CRC screen-
Table 1. Guidelines for Screening for Colorectal Cancer in Average-Risk Individuals*

<table>
<thead>
<tr>
<th>Organization</th>
<th>FOBT</th>
<th>FS</th>
<th>FOBT and FS</th>
<th>BE</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF¹</td>
<td>Annually</td>
<td>Yes, frequency unspecified</td>
<td>Yes, frequency unspecified</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AHCA²</td>
<td>Annually</td>
<td>Every 5 y</td>
<td>Annual FOBT and FS every 5 y</td>
<td>DCBE every 5-10 y</td>
<td>Every 10 y</td>
</tr>
<tr>
<td>AGA* (multi-disciplinary panel)</td>
<td>Annually</td>
<td>Every 5 y</td>
<td>Annual FOBT and FS every 5 y</td>
<td>Every 5 y</td>
<td>Every 10 y</td>
</tr>
<tr>
<td>ACG³</td>
<td>Annually</td>
<td>Every 5 y</td>
<td>Annual FOBT and FS every 5 y</td>
<td>DCBE every 5-10 y</td>
<td>Every 10 y</td>
</tr>
<tr>
<td>ACS¹</td>
<td>Annually</td>
<td>Every 5 y</td>
<td>Annual FOBT and FS every 5 y</td>
<td>Every 5 y</td>
<td>Every 10 y</td>
</tr>
<tr>
<td>WHO¹</td>
<td>NR</td>
<td>NR</td>
<td>Annual FOBT and FS every 3-5 y</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ACP¹</td>
<td>Yes (if patient refuses other options)</td>
<td>Every 10 y</td>
<td>NR</td>
<td>Every 10 y</td>
<td>Every 10 y</td>
</tr>
</tbody>
</table>

CTFPHE¹¹

*ACG = American College of Gastroenterology; ACP = American College of Physicians; ACS = American Cancer Society; AGA = American Gastroenterological Association; AHCA = Agency for Healthcare Policy and Research; BE = barium enema; CS = colonoscopy; CTFPHE = Canadian Task Force on the Periodic Health Examination; DCBE = double-contrast barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; NR = not recommended; USPSTF = US Preventive Services Task Force; WHO = World Health Organization.

The evidence that screening reduces mortality due to CRC is available from 3 randomized controlled trials (RCTs), 1 from the United States¹⁹ and 2 from Europe.¹⁶,¹⁷ The mortality reduction was 15% to 33% and was achieved by using annual or biennial screening with FOBTs (with and without rehydration). Similarly, the only RCT that showed a decrease in the prevalence of CRC by screening was the University of Minnesota FOBT trial.¹⁸ A 60% reduction in CRC mortality was suggested with screening FS.¹⁹,²⁰ In the National Polyp Study,²¹ colonoscopy and polypectomy resulted in a 76% to 90% estimated reduction in the prevalence of CRC, whereas a case-control study²² showed a 50% reduction.

Despite the efficacy of FOBT shown in RCTs, the plea for colonoscopy made by editorialists,²³,²⁴ professional groups,² and television personalities,²⁵ and the availability of screening tests, compliance is poor. A recent Centers for Disease Control and Prevention report revealed that only 19.8% of the surveyed population in 1997 had undergone FOBT during the preceding year, and only 30.4% had had sigmoidoscopy or proctoscopy during the preceding 5 years.²⁶ Compliance rates improved in 1999 (20.6% and 33.6%, respectively).²⁷ Use of colonoscopy as a screening test for CRC can be determined by considering the disadvantages of other screening tests and then the advantages of colonoscopy itself.

LIMITATIONS OF SCREENING TESTS FOR CRC

Fecal Occult Blood Test

Although FOBT is the only screening test for CRC that RCTs have shown mortality reduction¹⁵-¹⁷ and CRC inci-
dence reduction,\textsuperscript{13} it has several drawbacks. The recommended approach by the Agency for Healthcare Research and Quality is to use the nonrehydrated FOBT, whereas FOBT rehydration was emphasized in the University of Minnesota study as one of the reasons for its efficacy because rehydrating the FOBT cards increased the sensitivity to 80%.\textsuperscript{15} In a study comparing Hemocult with HemoQuant testing in patients being monitored after CRC resection, Hemocult testing (unrehydrated) yielded only a 35% sensitivity.\textsuperscript{28} A recent article that assessed the sensitivity of FOBT with colonoscopy as the gold standard found that only 23.9% of patients with advanced colorectal neoplasia had positive FOBT results.\textsuperscript{29} Even in first-degree relatives of patients with CRC, poor participation and compliance after a positive test result and lack of follow-up by physicians to evaluate a positive test result have been reported.\textsuperscript{30} Eventually, colonoscopy is needed to evaluate a positive FOBT result. The decrease in mortality in the University of Minnesota FOBT study could likely be attributed to the increased number of colonoscopies performed (with attendant polypectomy) because of rehydration of FOBT cards, which resulted in increased sensitivity but decreased specificity, i.e., more false-positive FOBT results.\textsuperscript{21} Thus, low sensitivity, low specificity, poor compliance, and the need for colonoscopy to evaluate a positive test result are disadvantages of FOBT.

**Barium Enema**

A single-contrast barium enema examination is not adequately sensitive for detecting colon adenomas.\textsuperscript{7} Additionally, double-contrast barium enema has not been shown to decrease CRC mortality or incidence. The National Polyp Study\textsuperscript{22} found that double-contrast barium enema detects only 48% of adenomas greater than 1 cm, whereas another study reported that double-contrast barium enema missed 67% of rectosigmoid polyps greater than 9 mm.\textsuperscript{33} Low sensitivity, lack of evidence of efficacy, and need for colonoscopy to evaluate positive test results are disadvantages of barium enema.

**Flexible Sigmoidoscopy**

No RCTs have reported a reduction in CRC mortality by FS. Two case-control studies of FS showed an 85% to 90% reduction in mortality due to distal CRC.\textsuperscript{19,20} Although not randomized, the study by Selby et al\textsuperscript{19} was important because it found a 30% overall reduction in CRC mortality in the group who underwent FS. This study also suggested that a 10-year interval between 2 screenings might be adequate. With use of rigid proctosigmoidoscopy, results have often been extrapolated to suggest that screening with a 60-cm flexible proctosigmoidoscope would have a similar effect in mortality reduction. The disadvantages of FS include inability to detect proximal adenomas and cancers, frequent lack of adequate preparation resulting in an unsatisfactory examination, lack of sedation with effect on patient comfort and consequently compliance, relatively infrequent performance by many primary care physicians, and a greater likelihood of missing clinically important neoplasms.\textsuperscript{7}

**FOBT and FS**

A 43% reduction in CRC mortality was reported in a nonrandomized controlled trial of people screened with FOBT and FS compared with FS alone.\textsuperscript{24} It was suggested that the associations of FOBT and FS with CRC mortality were independent.\textsuperscript{35} A substantially greater number of clinically important colorectal neoplasms were detected with FOBT and FS compared with FOBT alone in 2 different studies.\textsuperscript{36,37} However, the combined strategy of FOBT and FS still missed advanced colorectal neoplasms in 24% of patients compared with colonoscopy, even after rehydration of the FOBT cards.\textsuperscript{29}

**COLONOSCOPY AS A PRIMARY SCREENING STRATEGY FOR CRC**

Several published observations suggest that colonoscopy is a more suitable screening strategy for CRC compared with the other previously mentioned methods. The 60% to 70% reduction in CRC mortality noted in case-control studies that used rigid sigmoidoscopy could be extrapolated to colonoscopy,\textsuperscript{7} and the percentage of reduction should increase with a more complete bowel examination by colonoscopy.\textsuperscript{24} The National Polyp Study reported a 76% to 90% reduction in CRC incidence in a cohort of patients undergoing colonoscopy and polypectomy compared with reference populations.\textsuperscript{21} The CRC incidence in this cohort would have been higher than that in average-risk individuals because all these patients had adenomatous polyps. This study highlighted that clearing precursor adenomas lesions reduced subsequent CRC. Random screening of a segment of the population in Norway with FS and then with colonoscopy for those who had polyps reduced the incidence of CRC in the screening group significantly, resulting in a relative risk for CRC of 0.2 (95% confidence interval, 0.03-0.95; P = 0.002).\textsuperscript{28} Flexible sigmoidoscopy is not able to detect proximal adenomas and CRC. Retrospective and prospective studies of patients with CRC proximal to splenic flexure found no neoplasm distal to splenic flexure in nearly two thirds of patients.\textsuperscript{7} Similarly, 2 recent studies\textsuperscript{39,40} showed that, in asymptomatic individuals undergoing colonoscopy screening and those who had advanced proximal neoplasms, 62% and 52%, respectively, had no lesion in the colon distal to splenic flexure or only had hyperplastic polyps or small adenomas that would not have warranted colonoscopy. Currently, 40% of CRC in
the United States occurs proximal to splenic flexure, and there has been a gradual shift of CRC to the proximal colon during the past 30 years, especially in the elderly population. African Americans have also been reported to have a higher prevalence of right-sided lesions than other ethnic groups. Therefore, the entire colon must be inspected, and as mentioned previously, colonoscopy is the optimal screening test for viewing the entire colon.

Other potential benefits of colonoscopy as a primary screening strategy for CRC include (1) minimization of follow-up for patients in whom another screening test, such as FS or FOBT, showed positive results, which increases the convenience for the patient; (2) reduction in the indirect cost by decreasing the lost work time due to a single session; (3) longer interval because colonoscopy can be performed as infrequently as once every 10 years compared with once a year with FOBT or once every 3 to 5 years with FS; and (4) minimization of procedure-related discomfort by administration of sedation, which should improve patient satisfaction and compliance.7

EFFECT OF COLONOSCOPY SCREENING ON LIFE EXPECTANCY

Inadomi and Sonnenberg8 used declining exponential approximation of life expectancy, a mathematical model by which the effect of a medical condition on the life expectancy of an individual patient can be calculated, and a Markov model to examine the number of procedures required to achieve the calculated increase in the life expectancy with colonoscopy screening. They estimated that life extension with colonoscopy screening is 2 or 3 times longer than that with FS or FOBT, respectively.8

COST-EFFECTIVENESS OF COLONOSCOPY IN SCREENING FOR CRC

Cost-effectiveness is a stylized form of investment analysis in which returns on investment are measured in improvement in health rather than in dollars, and society as a whole is considered the relevant investor.14 A US government-sponsored panel recently concluded that cost-effectiveness analyses are intended to formulate decisions at the level of broad resource allocation and may provide little guidance about optimal bedside management of patients.14 Cost-effectiveness may be expressed in many ways: cost per year of life saved, cost per death prevented, cost per cancer prevented, cost per cancer detected, or, ideally, QALY as the summary effectiveness measure of choice. A cost-effectiveness of $40,000 per life-year saved (in 1997 dollars) is a benchmark cited as a common threshold below which an intervention is considered cost-effective.14 The economic analysis done by Wagner et al53 for annual FOBT, FS every 3 to 10 years, annual FOBT with FS every 3 years, and colonoscopy every 3 to 10 years found that the cost per life-year saved was $10,000, $8000 to $20,000, $10,000 to $15,000, and $9000 to $22,000, respectively.43 Thus, all strategies were relatively cost-effective. The incremental cost-effectiveness ratio assesses the cost-effectiveness of a particular strategy.44 It compares each screening strategy with the preceding less effective option, including a strategy of no screening. The incremental cost-effectiveness ratio is calculated as the difference in cost divided by the corresponding difference in effectiveness. The lower the ratio, the more effective the strategy. Using this method, Sonnenberg et al44 reported that colonoscopy performed every 10 years was the most cost-effective means of screening for CRC compared with annual FOBT or FS every 5 years because colonoscopy reduces mortality at low incremental costs. However, reporting the same incremental cost-effectiveness ratio, Frazier et al45 found annual rehydrated FOBT with FS every 5 years to be the most effective strategy among 22 different screening strategies, with an incremental cost-effectiveness ratio of $93,000 per year of life gained compared with annual nonrehydrated FOBT and FS every 5 years. The same study also reported that “screening for CRC, even in the setting of imperfect compliance, significantly reduces CRC mortality at costs comparable to other cancer screening procedures, and noted also that compliance rates significantly affect the incremental cost-effectiveness ratios.” Loeve et al,46 using an adapted version of a microsimulation model previously used to evaluate breast and cervical cancer screening, concluded that the induced savings by endoscopic CRC screening (FS every 5 years) would completely compensate for the costs. A recent summary of the evidence for the US Preventive Services Task Force assessing the effectiveness of different CRC screening tests for average-risk individuals stated that several options seemed to be effective, but the single best option could not be determined because data were insufficient.47

COMPLIANCE FOR COLONOSCOPY IN SCREENING FOR CRC

Compliance also plays an important role in the efficacy of a screening strategy. Rex et al48 described a study of colonoscopy offered free to asymptomatic medical personnel with negative FOBT results and observed that less than 15% invited by mail accepted the offer. However, Williams et al,49 in an adenoma follow-up study, reported that 90% of patients described colonoscopy as an acceptable procedure. Pignone et al50 found that few subjects opted for colonoscopy as a primary screening test when given information about various screening options. With efforts aimed at increasing awareness of the effectiveness of screening, compliance for CRC screening should increase, as has
occurred with both breast cancer and cervical cancer screening.

COMPICLATIONS OF COLONOSCOPY
A strong reservation for colonoscopy as a primary screening test is that it is invasive and hence associated with clinically important complications. In a study involving a well-defined population in a county in Sweden, the authors noted that the overall morbidity of colonoscopy was 0.4% (diagnostic colonoscopy, 0.2%; therapeutic colonoscopy, 1.2%). The study described 6066 colonoscopies; bleeding occurred in 0.2% and perforation in 0.1%, whereas no colonoscopy-related mortality occurred. The authors concluded that colonoscopy is safe and that the rate of adverse events was low. The complication (perforation) rate of FS was 1 in 25,000 procedures and much lower than that of colonoscopy. A similar perforation rate of 1 in 25,000 procedures was reported in the only study focusing on the complication rate of double-contrast barium enema, and the mortality rate associated with the complication was 1 in 250,000 in the same study. Detecting a proximal neoplastic lesion during colonoscopy saves 2.5 life-years for every major complication caused by colonoscopy, according to 1 model.

OTHER TECHNIQUES
Virtual colonoscopy or computed tomographic colography is a technique that is being used increasingly to detect adenomas, and the sensitivity to detect adenomas greater than 1 cm has been reported to be 75% to 90%. The current limitations of this strategy are the need for a thorough preparation of the colon, cost, lower sensitivity in detecting smaller adenomas, and inability to remove detected adenomas. Another important area in CRC screening is detecting DNA alterations in the exfoliated material from the neoplasm into the stool. Multiple DNA markers need to be assayed because of the genetic heterogeneity of CRC. Microsatellite instability markers, mutations on K-ras, adenomatous polyposis coli, and p53 genes and other markers are currently being studied in large-scale trials. The advantages of this strategy are noninvasiveness and good sensitivity and specificity in preliminary studies.

SUMMARY
An increasingly compelling case for colonoscopy as a primary screening strategy for CRC is being made. Based on the evidence previously outlined, the US Medicare program recently agreed to reimburse screening by colonoscopy, allowing an average-risk individual to be screened by colonoscopy once every 10 years after age 50 years. Inadomi and Sonnenberg estimated that a total of 3.9 million to 12.4 million colonoscopies would be needed to screen an entire US cohort from the age of 50 years until the age of 85 years.

Screening for CRC is a complex issue, and an ideal screening test has yet to be identified. The complexity is primarily due to the intrinsic interaction of various factors, including test sensitivity and specificity, efficacy, safety, cost-effectiveness, patient and physician compliance, and willingness of society or third-party payers to bear the cost. Because of the various screening tests currently available, both patients and physicians have choices. Based on recent literature, it appears that there is a subtle shift favoring colonoscopy for CRC screening. Multicenter studies evaluating computed tomographic colography are in progress, and large-scale studies exploring the potential for detecting colorectal neoplasms by using molecular markers obtained from stool samples are under way. Until such scientific information is available, the important message should be that every effort should be made by physicians to screen for CRC.

REFERENCES


