

Screening for Colorectal Cancer

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In 1993 Winawer [1] declared that colorectal cancer screening had come of age. Fifteen years later we have not yet achieved the goal of screening most of the eligible population despite the availability of multiple screening tests. Current screening rates in the United States are inadequate, with particularly poor rates in some segments of the population [2,3]. The Behavioral Risk Factor Surveillance System has reported that among people aged 50 years or older only 18.7% had a fecal occult blood test (FOBT) within the prior year, 50.6% had either flexible sigmoidoscopy or colonoscopy within the past 10 years, and 57.3% had one or both of these tests within these time periods [2]. In a national household survey using in-person interviews conducted by the National Health Interview Survey, about 50% of adults older than 50 years of age never had colorectal cancer screening and only 37.1% were current in their screening [3]. This study reported small variability in screening rates according to age and between men and women but reported large variability based on educational level, insurance availability, family history of colorectal cancer, and race, with black women less likely to be screened than white women. Somewhat surprising was the relatively low rate of colorectal cancer screening in the Medicare population despite the insurance coverage available for this screening and governmental efforts to increase screening in this population [4]. Results from randomized controlled clinical trials (RCT) have shown that with current technology, screening can greatly reduce colorectal cancer mortality and incidence [5–8]. The development and implementation of population-based screening programs has so far not successfully achieved what was envisioned in 1993.

In the United States, colorectal cancers represent 10% of incident cancers and cancer deaths [9]. About 6% of the population will develop colorectal cancer in their lifetime. In 2007, there will be an estimated 153,760 new cases and 52,180 deaths from colorectal cancer [9]. Globally, there are about 1 million new cases and about 500,000 deaths per year [10].

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In the United States, colorectal cancer is the third leading cause of cancer death among white, black, Asian/Pacific Islander, and Indian/Alaska Native men, but second among Hispanic men [11]. It is the second leading cause of cancer death among American women. In the United States, the colorectal cancer incidence rates are 60.4 and 44.2 per 100,000 population and the death rates are 23 and 16.1 per 100,000 population for men and women, respectively. Rates are generally higher in the Midwest and the Northeast.

The incidence has declined from about 60 per 100,000 in 1975 to about 50 per 100,000 in 2004. The decrease in colorectal cancer mortality in the United States has recently accelerated [11]. The rate decreased from about 29 per 100,000 population in 1970 to about 18 per 100,000 in 2004. The decline has been similar for men and women, although the decline for men began several years after that for women. Overall, the mortality among white men and women has declined by about 40%, but the mortality has changed little for black men and women. Since 1990, the mortality in blacks has decreased from about 30 to 25 per 100,000 population. The mortality has been consistently higher in men than women and since about 1980 the mortality has been higher in blacks than whites.

To further emphasize the importance of early detection, 5-year survival rates are strikingly different by stage, ranging from 90% for localized disease to 10% for distant disease, clearly arguing for early detection [11]. Five-year survival rates are similar for men and women, but are notably higher for whites than blacks; this difference may reflect in part the larger percentage of distant cancers in blacks compared with whites (24% versus 18%). For both sexes and all races, 5-year survival rates have increased from about 50% between 1975 and 1979 to 65% between 1996 and 2003, with a somewhat greater increase for white men and women than black men and women.

METHODS FOR COLORECTAL CANCER SCREENING

The American Cancer Society recommends several screening methods, ranging from stool blood tests to semi-invasive procedures, such as colonoscopy (Box 1) [12]. The recommendation to begin screening at age 50 for people at average risk is based on the age distribution of colorectal cancer rates, which shows a significant increase in the sixth decade of life. There is no specific evidence to suggest that the optimal effect of screening is achieved by starting at age 50 and continuing indefinitely, however. Recently, in the United Kingdom, colorectal cancer screening has been recommended for average-risk people aged 60 to 69 [13].

The guaiac-based fecal occult blood test (Hemoccult) is the only screening test proved to be effective by RCTs [5–8,14–18]. Other screening tests, such as immunochemical-based fecal occult blood tests, although never tested in an RCT, have been evaluated against guaiac-based tests and have performed at least as well, with higher compliance rates [19–23]. Colorectal cancer is the only cancer for which the diagnostic test, colonoscopy, is recommended as a screening test.

Box 1: Recommendations from the American Cancer Society

Beginning at age 50, men and women should follow one of these five testing schedules:

Yearly fecal occult blood test (FOBT)^a or fecal immunochemical test (FIT)

Flexible sigmoidoscopy every 5 years

Yearly FOBT^a or FIT, plus flexible sigmoidoscopy every 5 years^b

Double-contrast barium enema every 5 years

Colonoscopy every 10 years

All positive tests should be followed up with colonoscopy

People should talk to their doctors about starting colorectal cancer screening earlier or undergoing screening more often if they have any of the following colorectal cancer risk factors:

A personal history of colorectal cancer or adenomatous polyps

A strong family history of colorectal cancer or polyps (cancer or polyps in a first-degree relative [parent, sibling, or child] younger than 60 or in two first-degree relatives of any age)

A personal history of chronic inflammatory bowel disease

A family history of a hereditary colorectal cancer syndrome (familial adenomatous polyposis or hereditary nonpolyposis colon cancer)

^aFor FOBT, the take-home multiple sample method should be used.

^bThe combination of yearly FOBT or FIT and flexible sigmoidoscopy every 5 years is preferred over either of these options alone.

FECAL OCCULT BLOOD TESTS**Guaiaac-Based Tests**

The only screening test for colorectal cancer that has been proved to be effective is the guaiac-based Hemoccult test, which detects the pseudoperoxidase activity of heme. Fecal excretion of heme as a screening test is based on the propensity of colon cancers and adenomas to bleed microscopically. The test must be performed multiple times on multiple occasions to be sensitive, however, because of the intermittent nature of this bleeding. Three RCTs conducted in the United States, England, and Denmark have demonstrated that multiple testing with Hemoccult applied annually and biennially significantly reduces colorectal cancer mortality [5–7]. One of the trials further demonstrated that such screening reduces the cancer incidence [8]. A recent Cochrane Review concluded from a review of the three RCTs and unpublished data from a Swedish trial that biennial screening with the Hemoccult test reduced mortality by 16% overall, or by 25% when adjusted for missed screening appointments [24].

These three RCTs used Hemoccult as the screening test, generally screened men and women between the ages of 45 and 80 years, incorporated some form of dietary restriction, used colorectal cancer mortality as the primary endpoint, and included a biennial test group. The results from all three trials were

consistent and statistically significant. In a fourth, unpublished RCT, the Hemoccult test performed on men and women aged 60 to 64 years living in Sweden revealed a similar 16% reduction in mortality, as reported by Hewitson and colleagues [24,25]. A study in which geographic areas rather than individuals were randomized to evaluate the Hemoccult test on men and women aged 45 to 74 years also reported a 16% colorectal cancer mortality reduction from biennial screening [26]. The mortality reduction was 33% for compliers, who completed at least one screen.

Despite the deficiencies that guaiac-based tests are not specific for human blood and that not all cancers or adenomas bleed, the Hemoccult test has consistently been shown to reduce mortality when applied repeatedly over time, either annually or biennially, in an average-risk asymptomatic population between the ages of 45 through 80 years. Several observational studies showed similar results. Immunochemical tests seem to be superior to guaiac-based tests to detect fecal occult blood and would therefore be expected to also demonstrate a beneficial effect.

Immunochemical Tests

Immunochemical tests use monoclonal or polyclonal antibodies to detect the globin protein in human hemoglobin [27]. These tests do not react with non-human hemoglobin or with foods that contain peroxidase activity and are therefore more specific than guaiac tests. They detect only human hemoglobin from the lower, not the upper, gastrointestinal tract [28]. There has been no RCT of a fecal immunochemical test (FIT), but there have been numerous observational studies, including studies comparing an immunochemical test to Hemoccult.

In a paired comparison of Hemoccult and Insure, a fecal immunochemical test, FIT was more sensitive for cancers and significant adenomas [21]. For the FIT, the subject sampled the stool surface by swishing the brush over the stool and then wiping the brush onto the test card, as opposed to collecting a direct stool sample for the Hemoccult test. In a comparison of Insure with Hemoccult Sensa and FlexSure OBT, the participation rate was highest for Insure, which was likely because of the simplified sampling technique and lack of dietary restrictions [19]. Another study of Insure showed that the sensitivity and specificity could be adjusted to increase sensitivity but at the cost of reduced specificity [29]. Quantitative FITs have the advantage of calibration of positivity to adjust the population-based screening program according to the funding level. Applying FIT to patients scheduled for colonoscopy, Levi and colleagues [30] showed the advantages of a quantitative test to determine the cutoff for positivity. The investigators varied the hemoglobin level for a positive test from 50 to 150 ng/mL using three fecal samples and computed sensitivity and specificity for different levels. The average fecal hemoglobin levels increased from normal mucosa through non-advanced adenoma and advanced adenoma to cancer. The fecal hemoglobin level in the most non-advanced adenomas was less than 75 ng/mL.

Screening with a 1-day immunochemical hemagglutination test (Immudia-Hem Sp or HemSelect; Fujirebio, Tokyo, Japan) was introduced in Japan in 1986 and evaluated by case-controlled studies that showed colorectal cancer mortality reductions of up to 80% [31–33]. In Japan, 6 million people, representing 17% of the eligible population, have been screened with immunochemical tests [34]. The positivity rate was 7.1% (N = 430,000). Sixty percent of test positives complied with the diagnostic protocol, which consisted of colonoscopy, or flexible sigmoidoscopy and double contrast barium enema. The colorectal cancer detection rate was 1.6 per 1000 population, with 69% of cancers being Dukes A and 14% being Dukes B, suggesting that the program worked well in detecting early cancer. In a cohort of more than 40,000 men and women in Japan, colorectal cancer mortality was reduced by 72% and colorectal cancer incidence was reduced by 59% in subjects screened with an immunochemical test compared with unscreened controls [35].

Other countries that have evaluated immunochemical tests, such as Korea, China, Israel, Australia, and Italy, have generally concluded that these tests perform better than guaiac tests [22,36–42]. The Scottish Bowel Screening Program adopted a two-tiered screening program using an immunochemical test on guaiac-positive patients that seemed to reduce the number of colonoscopies and the overall cost of screening [43].

The Multisociety Task Force on Colorectal Cancer recommends annual screening using a guaiac test with dietary restrictions or an immunochemical test without dietary restrictions [44]. The American Cancer Society has a similar recommendation, but advises that immunochemical tests are more acceptable to patients and are likely to perform as well or better than guaiac tests [12]. The available data indicate that immunochemical tests perform better than guaiac tests, but cost more.

OTHER MARKERS

DNA in Stool and Blood

Fearon and Vogelstein [45] described early DNA mutations in colorectal cancer, such as K-ras and APC mutations, and later mutations, such as p53 and BAT-26 mutations. Mutations detected in stool DNA have been investigated as a biologic marker for colorectal cancer, but this involves separating minute amounts of abnormal human DNA from normal human DNA and bacterial DNA in stool, amplifying them, and then testing for and detecting the correct genetic molecular markers [46]. Advances in techniques, such as polymerase chain reaction (PCR), assist in this detection. Advantages of stool DNA include that the DNA is shed continuously and can be detected in minute amounts by PCR. Early results were promising. In a pilot study of stored frozen stool from 22 patients who had colorectal cancer, 11 patients who had adenoma, and 28 patients who had normal colons, Ahlquist and colleagues [47] reported a sensitivity of 91% for cancer and 82% for adenomas using an array of DNA markers. These results were not reproduced in subsequent studies; the

sensitivity using all the markers was 50% to 60% for cancer and even lower for adenomas [48–51]. Imperiale and colleagues [50] using a DNA panel of 21 mutations detected only 52% of cancers and 13% of advanced adenomas. Because of a relatively high cost, cumbersome collection process, and relatively low sensitivity, stool DNA cannot be recommended for population-based screening [52,53]. Further work is needed to improve the collection method and develop the best panel of markers to improve test sensitivity.

A recent study by Itzkowitz and colleagues [54] showed considerable improvement using improved DNA stabilization and isolation techniques to better preserve and purify the stool DNA and an improved promoter methylation marker; they reported an 87.5% sensitivity and 82% specificity for cancer regardless of cancer stage or location. Other studies involving small numbers of patients and using blood rather than stool have shown similar promising results, but confirmation is needed in larger clinical studies to develop an appropriate strategy for DNA testing for colorectal cancer and adenomas [55–58].

FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy every 5 years with or without annual fecal occult blood testing beginning at age 50 is recommended despite the absence of an RCT demonstrating effectiveness [12,44,59]. Arguments favoring this strategy are based largely on the biology of colorectal cancer and a few observational studies, but such studies generally provide biased estimates of the screening effect [60]. The biology is based on removing adenomas that are the usual precursors of colorectal cancer [61–65]. The reduction in incidence and mortality is unknown. The Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO), an RCT in which two flexible sigmoidoscopies at baseline and either 3- or 5-year intervals were offered to those in the screened group, should provide data on the mortality reduction from this mode of screening [66]. Only adenomas and early cancers within reach of the sigmoidoscope and synchronous lesions can be detected; this includes only one half to three quarters of all adenomas and cancers in the colon [67–70].

Estimates of the benefit of flexible sigmoidoscopy have come largely from case-control studies [71–74]. Selby and colleagues [71] found screening sigmoidoscopy reduced colorectal cancer by 59% in the descending colon, whereas Newcombe and colleagues [72] reported a reduction of 70% in the incidence of distal cancers in patients reporting a single flexible sigmoidoscopy and of 76% in those who had one or more flexible sigmoidoscopies. Two studies suggest that about half of significant lesions may be missed by flexible sigmoidoscopy screening. In a study of colonoscopy in 3121 adults, 52% of patients who had advanced proximal lesions would have been missed if they had been screened by flexible sigmoidoscopy alone [69]. Imperiale and colleagues [70] in a colonoscopy study of 1994 adults found that about half of patients who had significant proximal lesions had no distal polyps.

No RCTs have analyzed colorectal cancer mortality reduction from flexible sigmoidoscopy combined with FOBT. One study reported a somewhat larger

reduction in colon cancer with rigid (not flexible) sigmoidoscopy and guaiac FOBT as compared with rigid sigmoidoscopy alone [75]. Two RCTs found that combined flexible sigmoidoscopy and FOBT detected four to five times more large polyps and cancers than FOBT alone [76,77]. In another trial, however, more polyps and cancers were not diagnosed in patients who had both FOBT and flexible sigmoidoscopy versus only flexible sigmoidoscopy [78]. Hendon and DiPalma [79] found that the detection of advanced neoplasia by flexible sigmoidoscopy alone was 70%, but the detection rate increased to 76% with the addition of FOBT because of identification of proximal lesions.

Flexible sigmoidoscopy screening, if proven effective in reducing colorectal cancer mortality, has some advantages over colonoscopy. It can be performed by primary care physicians and possibly nurse endoscopists in addition to gastroenterologists or other specialists [80]. Based on an American survey, Brown and colleagues [81] found that 65% of sigmoidoscopy procedures were performed by primary care physicians, 25% by gastroenterologists, and 10% by general surgeons. In a recent Canadian study, nurses capably performed flexible sigmoidoscopies to screen about 1800 asymptomatic men and women older than 50 years of age [82]. Positive results were followed by colonoscopy performed by gastroenterologists. In the PLCO Trial some centers used nurse endoscopists to perform flexible sigmoidoscopy with good results based on quality assurance parameters [66].

Flexible sigmoidoscopy screening should reduce colorectal cancer mortality but the magnitude of the reduction remains to be determined from ongoing trials. This screening method does, however, miss some proximal lesions in individuals who have no index distal lesion to warrant colonoscopy [69]. Results vary according to several factors, including gender and ethnicity. Miss rates were higher in women than men [83–85]. Francois and colleagues [86] on follow-up of individuals who had a positive flexible sigmoidoscopy found neoplasms in the proximal colon in 64% of Caucasians, 60% of African Americans, 67% of Hispanics, and 26% of Asians. Asians had a much higher rate of distal lesions compared with the other ethnic groups.

Quality control is essential. In the Norwegian Colorectal Cancer Prevention Study, a randomized controlled trial of one-time flexible sigmoidoscopy, detection rates varied among endoscopists from 36.4% to 65.5% for any polyp, from 12.7% to 21.2% for any adenoma, and from 2.9% to 5.0% for advanced lesions [87].

In a Markov model to simulate the progression of a cohort of asymptomatic average-risk individuals 55 to 64 years of age, flexible sigmoidoscopy screening was more efficient in cost per life-year saved than either FOBT or colonoscopy [88]. In the absence of good data, however, assumptions must be made about the benefit. This model was based on data from a nonrandomized, uncontrolled, community-based flexible sigmoidoscopy screening program. Furthermore, the various models of cost effectiveness are different and none have adequately measured the true costs of a screening program [89]. These studies should be interpreted cautiously pending a better understanding of the

effectiveness of flexible sigmoidoscopy screening. Another consideration is the increasing incidence of right-sided lesions with increasing age [90–92].

COLONOSCOPY

The modest increase in colorectal cancer screening between 2000 and 2003 is largely attributable to increased use of colonoscopy for screening that was significant among all populations except for low-income, insured patients without Medicare coverage [93]. Despite no RCTs of colonoscopy screening, colonoscopy was proposed years ago as either a one-time or periodic screening test [84,94–97]. The National Polyp Study in 1993 demonstrated the importance of polypectomy in preventing colorectal cancer. This study showed a 76% to 90% reduction in the incidence of cancer in patients who had one or more adenomas removed [61]. Recently this group reported a 69% reduction in colorectal cancer mortality over the expected mortality in the adenoma group [98].

Evidence of effectiveness of colonoscopy screening is provided by the FOBT trials that used colonoscopy as the diagnostic test and by cohort studies, such as the National Polyp Study and the Italian Multicenter Study, that showed reductions in colorectal cancer incidence among patients who had adenomas detected and removed [61,99]. In a mathematical model of life expectancy with screening, the estimated extension of life by colonoscopy screening is two times longer than that with flexible sigmoidoscopy and three times longer than that with FOBT [100].

Screening by colonoscopy has negative aspects. Even though it is the gold standard, colonoscopy can miss lesions, particularly from incomplete procedures [101–106]. Factors associated with incomplete colonoscopy include increased patient age, female gender, and procedure performance in a private office [105].

In a review of studies of tandem or back-to-back colonoscopies, on average 21% of adenomas were missed [107]. Of these adenomas, 26% were 1 to 5 mm and 2% were 10 mm or more. In a study of 7882 colonoscopies performed by 12 experienced gastroenterologists, including 25% that were first-time screening examinations, the mean withdrawal time was related to detection rates [108]. Colonoscopies with withdrawal times of 6 minutes or more had a more than twofold higher detection rate than colonoscopies with withdrawal times less than 6 minutes (28.3% versus 11.8% for all neoplasms, and 6.4% versus 2.6% for advanced neoplasms). Furthermore, the yield varied greatly among the 12 gastroenterologists, suggesting that some gastroenterologists missed up to half of the lesions, including larger ones.

The highly variable performance of screening colonoscopy by gastroenterologists could be reduced through improvements in technology, such as chromoendoscopy, autofluorescence, Third-Eye Retroscope, and wide-angle colonoscopy, but the time and costs of colonoscopy would increase [109]. For optimal colonoscopy, the colonoscopist should obtain an effective and safe bowel preparation and be sufficiently slow and careful during colonoscopic withdrawal to identify all adenomas. Rex [110] provides an excellent review of

studies on colonoscopy outcomes and suggests that suboptimal technique is a significant contributor to missed lesions.

Trecca and colleagues [111] showed that chromoendoscopy detected lesions with advanced histology that were missed by conventional colonoscopy, particularly nonpolypoid, flat lesions. They recommended selection of chromoendoscopy when optical colonoscopy provides clues of nonpolypoid lesions. Stergiou and colleagues [112] showed that zoom chromoendoscopy increased the detection rate of polyps at the cost of longer retrieval time.

Because the lifetime prevalence of colorectal cancer is about 6%, the vast majority (94%) of people who receive a screening colonoscopy do not need it. They incur the cost and risks of the procedure, including anesthesia risks, hemorrhage, and perforation, with no direct benefit. Lieberman and colleagues [69] reported that 0.3% (10 out of 3121) patients had major complications, including bleeding, myocardial infarction, and stroke [113]. Three patients died within 1 month of the procedure. Imperiale and colleagues [70] reported that 1 (0.05%) of 1994 people undergoing screening colonoscopy had a perforation that did not require surgery and 3 (0.15%) had bleeding that required treatment in an emergency department. Dafnis and colleagues [114] found that 0.4% of 6066 colonoscopies resulted in a complication, mainly bleeding and perforation. No deaths were attributed to the procedure. The overall complication rate is between 1 and 3 per 1000 colonoscopies [5,115–123]. Postpolypectomy bleeding and delayed bleeding are probably underreported [124]. In a study of more than 16,000 patients older than age 40 undergoing colonoscopy, mostly not for screening, the serious overall complication rate (procedure-related event leading to hospitalization) was 5.0 per 1000 colonoscopies, with a higher rate for colonoscopies with biopsy or polypectomy compared with colonoscopies without biopsy or polypectomy (7.0 versus 0.8 per 1000) [125].

The benefit from colonoscopic screening is unknown. Initially believed to be substantial [61,99], recent data have indicated that the benefit may be less than originally believed [73,103,104]. Problems of incomplete colonoscopies and frequently missed lesions raise concerns and prompt calls for quality improvement. Chromoendoscopy might help improve the quality of colonoscopy but it increases procedure time and cost. Wide-angle colonoscopy has not yet been shown to improve detection rates [126,127]. Preliminary data on computer-assisted colonoscopy (NeoGuide Endoscopy System) based on 11 patients showed some promise, but more data are needed to determine whether this method reduces colonic looping, improves safety, and enhances detection rates [128].

CT COLONOGRAPHY (VIRTUAL COLONOSCOPY)

CT colonography is a noninvasive imaging procedure that creates a three-dimensional image of the colon by combining multiple helical CT scans with the help of a computer program [27]. Patients found to have a significant lesion must be referred for colonoscopy. CT colonography did not perform well, particularly for smaller lesions, in early studies [129], but a subsequent

well-designed study showed it can be excellent if performed under optimal circumstances [130]. This study using three-dimensional imaging reported sensitivities of 93.8% for polyps at least 10 mm in diameter, 93.9% for polyps at least 8 mm, and 88.7% for polyps at least 6 mm. These sensitivities were somewhat greater than those for colonoscopy for the two groups of larger-diameter polyps. The specificities were 96.0%, 92.2%, and 79.6% for the three groups of polyps, respectively. This study showed that CT colonography was an accurate method for detecting adenomatous polyps. An accompanying editorial identified factors unique to this study that could account for the unusually good performance of CT colonography [131]. Cotton and colleagues [132], however, presented results indicating that CT colonography was not ready for widespread use. In this study, the sensitivities were 39% and 55% and specificities were 90.5% and 96% for lesions at least 6 mm and 10 mm in diameter, respectively. Conventional colonoscopy performed much better than CT colonography, with sensitivities of 99% and 100% for the different lesion sizes. These two studies show the potential of CT colonography as a useful screening tool if done under ideal circumstances but expose the significant deficiencies of the test when performed under general practice conditions.

Patients who have significant lesions on CT colonography must undergo optical colonoscopy. Ideally, performing optical colonoscopy following a positive CT colonography on the same day would avoid the patient's taking a second colonic preparation. This plan, however, requires considerable coordination and is not generally done in screening programs.

A meta-analysis of 24 studies involving 4181 patients found high and consistent sensitivities and specificities for polyps 1 cm or larger, but much lower values for smaller polyps [133]. CT colonography detected 96% of colorectal cancers. A meta-analysis of 33 studies involving more than 6000 patients found wide variation in sensitivity among studies particularly related to polyp size but little variation in specificity; the authors concluded that the variability in sensitivity needs to be resolved before recommending CT colonography for mass screening [134]. In a meta-analysis of 30 CT colonography studies, the sensitivity was higher for larger than smaller polyps, two-dimensional and three-dimensional CT colonography performed about equally well, CT colonography was superior to air-contrast barium enema, and optical colonoscopy performed better than CT colonography for small polyps [135]. CT colonography thus performs well in identifying larger lesions, particularly those larger than 1 cm, and reasonably well for those larger than 0.6 cm. This level of performance might be sufficient because these polyps are the more clinically significant ones [136].

The rate of complications is relatively small [137]. Based on data from 50 centers in the United Kingdom representing 17,067 CT colonographic examinations, potentially serious events occurred in 0.08% of the symptomatic patients, with no deaths. Vijan and colleagues [138] reported that CT colonography was cost effective compared with no screen but was more expensive and less effective than optical colonoscopy. Pickhardt and colleagues [139]

found that CT colonography with a 6-mm threshold was more cost effective than flexible sigmoidoscopy or optical colonoscopy.

CAPSULE ENDOSCOPY

Capsule endoscopy (CE), a wireless capsule containing a miniaturized camera, a light source, and a wireless circuit for acquiring and transmitting signals, provides about two pictures per second for up to 8 hours after swallowing as it travels through the small intestine [27]. It is an outpatient procedure that can be used to detect lesions in the small intestine, but it cannot take biopsies or perform therapeutic procedures [140]. Its primary use is in evaluating patients who have bleeding that remains obscure after nondiagnostic upper and lower endoscopies [141]. The capsule is typically passed per rectum in 1 to 2 days. It is generally safe, with few complications [142]. Symptomatic capsule retention occurs in less than 2% of examinations.

The interpretation time for a full 8-hour video is between 45 and 120 minutes [143]. It is primarily used to diagnose small bowel pathology, but it has been considered for colorectal cancer screening. In a pilot study, 41 patients scheduled for screening colonoscopy or colonoscopic evaluation of symptoms were also evaluated with CE [144]. CE identified 19 of the 25 patients who had positive findings, and 10 of the 13 patients who had significant findings (polyp >6 mm or three or more polyps). CE detected seven lesions in people who had a negative colonoscopy. Sensitivity of CE for significant lesions was 77%, specificity was 70%, and positive predictive value was 59%. There were no adverse events from CE. These results suggest CE may hold promise for CRC screening but more data are needed.

DOUBLE CONTRAST BARIUM ENEMA

Although double contrast barium enema (DCBE) is recommended for CRC screening, there are no randomized controlled trials of its efficacy, only observational studies [12,145–147]. Scheitel and colleagues [145] in a case-controlled study reported a 33% reduction in colorectal cancer mortality. Rex and colleagues [146] found the sensitivity of DCBE for cancer was 85% compared with 95% for colonoscopy. In a study comparing DCBE to colonoscopy, Winawer and colleagues [147] found that the sensitivity of DCBE (using colonoscopy as the standard) was only 32% for polyps less than 0.5 cm, 53% for polyps 0.6 to 1.0 cm, and 48% for polyps greater than 1 cm. DCBE was positive in 83 of 470 patients (specificity = 85%) who had no polyps found on colonoscopy. Because of its relatively poor performance, DCBE should only be used when colonoscopy is unavailable or contraindicated [148].

The risks of DCBE are relatively low [149]. Only about 1 in 10,000 examinations result in important complications, including one perforation in 25,000 examinations, and one death in 55,000 examinations [150]. Its value for screening and diagnosis has diminished as better technology has emerged. It is still occasionally used because it is a fairly inexpensive and simple test [151].

SUMMARY

Although there are several methods available for colon cancer screening, none is optimal. Colonoscopy screening for the 70 million people older than 50 years of age in the United States could cost \$10 billion per annum and exceed the physician capacity to perform this procedure [152,153]. A simple, inexpensive, noninvasive, and relatively sensitive screening test is needed to identify people at risk for developing advanced adenomas or colorectal cancer who would benefit from colonoscopy. The FOBTs could accomplish this, but they are too inaccurate; hence, too many people are referred for unnecessary colonoscopy and too many are not referred for necessary colonoscopy. It is hoped that new markers will be identified that perform better. Until then we fortunately have a variety of screening strategies that do work.

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