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Screening for colon cancer

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Abstract

Colorectal cancer screening reduces mortality in individuals 50 years and older. Each of the screening tests currently available has advantages and limitations, and there is no consensus as to which test or combination of tests is best. What is clear, however, is that the rates of colorectal cancer screening remain low. This review summarizes the clinical evidence supporting colorectal cancer screening in the average risk population and in high risk groups, discusses the advantages and disadvantages of the available screening tests, outlines the currently recommended guidelines for screening based on risk category, and discusses new and emerging technologies for colorectal cancer screening.

Keywords: *Neoplasms; polyps; colon; colonoscopy; rectum.*

Introduction

Colorectal cancer is the third most common cancer throughout the world, with more than one million new cases diagnosed each year[1], and it is the second leading cause of cancer death in the United States. Last year in the United States alone, more than 145 000 people were diagnosed with colorectal cancer and more than 56 000 died of their disease[2]. Fortunately, this neoplasm is highly suited to screening because of its long preclinical phase, during which it is detectable and curable[3]. Nevertheless, screening programs for colorectal cancer have been only partly successful, owing largely to poor patient compliance with screening recommendations[4–7]. A number of organizations including the World Health Organization (WHO), the American Cancer Society (ACS), the US Agency for Health Care Policy and Research (USAHCPR), and the US Preventive Service Task Force (USPSTF) have issued or endorsed guidelines for colorectal cancer screening[8–10].

Average risk population

Average risk patients are asymptomatic individuals 50 years of age or older who have no personal or family history of colorectal cancer or adenomatous polyps and no history of inflammatory bowel disease. The most recently published screening recommendations of the ACS[8], the USAHCPR[9] and the USPSTF[10] present guidelines for screening average risk patients in the form of lists of options (Table 1). The options include annual (or biennial) fecal occult blood test, flexible sigmoidoscopy every 5 years, annual fecal occult blood test plus flexible sigmoidoscopy every 5 years, double contrast barium enema every 5 years, and colonoscopy every 10 years.

Fecal occult blood testing

Fecal occult blood testing (FOBT) is the safest and least expensive of the currently available screening tests. Three prospective, randomized, controlled trials have demonstrated the effectiveness of serial FOBT in reducing colorectal cancer mortality by 15%–33%[11–14]. However, its benefit in reducing colorectal mortality is attributed not only to early cancer detection but also to the incidental discovery and removal of adenomatous polyps at subsequent colonoscopy, which is recommended for patients with a positive FOBT. Such chance discovery of adenomatous polyps and non-bleeding cancers by colonoscopy has been estimated to account for 16%–25% of the colorectal cancer deaths prevented by the use of FOBT[15]. Nevertheless, one national study

showed that only one-third of individuals with a positive FOBT currently undergo colonoscopy[16]. Limitations of FOBT include its relatively low sensitivity for detecting cancers and its inability to detect the vast majority of adenomas[17]. Because colorectal cancers bleed intermittently, 50% or more of patients with colorectal cancer may have a negative test result[17,18]. Thus, to be effective, FOBT must be administered annually or biennially, which makes patient compliance a problem. Furthermore, the positive predictive value of standard FOBT is only approximately 10%[17,18].

The most widely used test in the United States, Hemoccult II, is a guaiac-based test that detects the pseudoperoxidase activity found in hemoglobin after application of hydrogen peroxide to the stool sample. It requires that the patient apply to six test card windows two separate samples from three different stools. The test is not specific for human hemoglobin, and dietary substances can result in false positive and false negative examinations[19–21]. Rehydration of the test samples before applying hydrogen peroxidase to the test windows increases sensitivity, but is not recommended[9] because it increases the false positive rate, thus reducing the positive predictive value by more than 50%[11]. Newer guaiac-based and immunochemical FOBT tests (see section on New and emerging technologies) have improved sensitivity with maintenance of acceptable specificity[22,23].

Flexible sigmoidoscopy

Data from four case-control studies support the effectiveness of flexible sigmoidoscopy in reducing colorectal cancer mortality[24–27]. Individuals in these studies who had undergone at least one screening sigmoidoscopy during the previous 10 years had only 21%–30% the risk of developing fatal colorectal cancer as control subjects. Compared with colonoscopy, flexible sigmoidoscopy is less expensive and has a lower complication rate (approximately 1–2 perforations per 10 000 examinations)[28,29]. In addition, it requires a less rigorous bowel preparation and does not require sedation. The major disadvantage of flexible sigmoidoscopy, however, is that it examines only a portion of the colon, thereby enabling detection of only approximately 50% of colonic lesions[30,31]. If a polyp is detected at sigmoidoscopy, colonoscopy may be needed to evaluate the entire colon, but the decision to perform colonoscopy should be individualized[9]. Factors associated with increased risk of advanced proximal neoplasia include age greater than 65 years, a family history of colorectal cancer, and distal adenomas that are ≥1 cm, multiple or contain villous histology[32–34]. In a randomized control trial, colonoscopy after detection of one or more polyps at screening sigmoidoscopy resulted in an 80% reduction in colorectal cancer incidence[35]. Nevertheless, proximal advanced adenomas (those ≥10 mm or containing villous histology, high-grade dysplasia or invasive cancer) also occur in approximately 2%–5% of individuals without distal adenomas[32–34,36], underscoring the major limitation of screening sigmoidoscopy. A recent study of asymptomatic women who underwent screening colonoscopy showed that only 35% of those with advanced neoplasia would have had their lesions identified had they undergone flexible sigmoidoscopy alone[37].

Fecal occult blood testing combined with flexible sigmoidoscopy

The rationale for combining FOBT with flexible sigmoidoscopy is two-fold: (1) approximately half of the cancers missed by FOBT would be detected at sigmoidoscopy, and (2) FOBT is insensitive for detecting adenomas, many of which would be detected at sigmoidoscopy. Two randomized control trials have reported a 3–5-fold increase in the number of large adenomas and cancers detected when one time FOBT plus sigmoidoscopy are performed compared with one time FOBT alone[38,39]. Nevertheless, there is little direct evidence to support such a combined approach over annual or biennial FOBT, which is more sensitive than a one time test. Furthermore, a large number of colonic adenomas and carcinomas are not within the reach of the sigmoidoscope. Although some of these lesions would be detected when a positive sigmoidoscopy leads to a follow-up colonoscopy or barium enema, many of them would be missed, as up to 50% of proximal colonic cancers are not associated with a distal adenoma[34,40–44]. One study demonstrated that one-time screening with FOBT plus sigmoidoscopy failed to identify about one-quarter of subjects with advanced neoplasia and one half of subjects with advanced proximal neoplasia[44].

Colonoscopy

Colonoscopy is the only colorectal cancer screening test that allows evaluation of the entire colon and provides the opportunity to remove polyps and small polypoid cancers at the same time. Although there are no controlled trials demonstrating that screening colonoscopy alone reduces colorectal cancer incidence or mortality in those at average risk for the disease, indirect evidence for the effectiveness of colonoscopy comes from one case control study[29] and several cohort and observational studies[45–48]. The case control study showed a 40%–50% reduction in colorectal cancer incidence in individuals who had undergone colonoscopy or polypectomy[29]. In addition, it is reasonable to extrapolate to colonoscopic screening the evidence of reduced colorectal cancer mortality shown with screening sigmoidoscopy[24,25]. Limitations of colonoscopy, however, are its greater cost and risk compared with other screening tests. Perforation occurs in approximately 1 in 1000 colonoscopies, major

bleeding occurs in approximately 3 per 1000, and 1–3 individuals in 10 000 undergoing colonoscopy die of complications from the procedure[28,41,49–51]. In addition, colonoscopy is incomplete in 5%–15% of individuals[40,41,49].

As stated previously, the advantage of colonoscopy over sigmoidoscopy is that approximately half of patients with advanced proximal neoplasms have no distal colonic neoplasms[33,34,37,52]. The rationale for the recommended 10-year interval for colonoscopic screening is based on the relatively high sensitivity of colonoscopy for polyp detection and the relatively long period of time required for most adenomatous polyps to transform into cancers, estimated to be at least 10 years, on average[53]. A study of back-to-back colonoscopies[54] and a study comparing colonoscopy and computed tomography colonography[55] have shown colonoscopy to have a sensitivity of 88%–94% for adenomas ≥1 cm.

Barium enema examination

For many years the double contrast barium enema (DCBE) was the only radiologic alternative to colonoscopy for colorectal cancer detection. Similar to colonoscopy, barium enema examination is a test that allows evaluation of the entire colon in approximately 90%–95% of patients[56–58]. No data are available on the sensitivity of DCBE in an average risk screening population. However, a screening study of patients at higher than average risk for colorectal neoplasia showed a 39%–56% sensitivity for polyps ≥1 cm for three independent readers[59]. The National Polyp Study in the United States demonstrated a sensitivity for DCBE of approximately 50% for ≥1 cm polyps in patients undergoing surveillance after removal of adenomatous polyps[60]. A study comparing colonoscopy, DCBE and computed tomography colonography reported a sensitivity of DCBE for ≥1 cm polyps of 45%[61]. In a non-randomized retrospective study of over 2000 consecutive patients with colorectal cancer in community practice, the sensitivity for cancer was 85% with DCBE and 95% with colonoscopy[62]. The major disadvantages of DCBE are its relatively low sensitivity for polyps ≥1 cm and the need for subsequent colonoscopy for polyp removal after a positive study. Its advantages compared to colonoscopy are that it is safer (approximately 1 perforation in 25 000 procedures)[63], less expensive, and does not require sedation.

Cost effectiveness

Most studies of the cost-effectiveness of FOBT (every 1–2 years), flexible sigmoidoscopy (every 5 years), colonoscopy (every 10 years) and double contrast barium enema examination (every 5–10 years) have shown costs per life-year saved of less than $25 000[64–68]. These figures compare favorably with estimates of cost per life-year saved for breast cancer, cervical cancer and hypertension screening programs, which range from approximately $9000–$50 000[69,70].

Screening recommendations (Table 1)

Recommended options for colorectal cancer screening of asymptomatic individuals of average risk include the following (beginning at age 50): annual FOBT (if positive, examine entire colon with colonoscopy or with sigmoidoscopy plus DCBE if colonoscopy is not available), flexible sigmoidoscopy every 5 years (followed by colonoscopy in most cases if adenomatous polyp or cancer found), annual FOBT and sigmoidoscopy every 5 years, colonoscopy every 10 years, or DCBE every 5 years.

Table 1   *Recommended options for colorectal cancer screening in asymptomatic, average-risk individuals*[8–10]

Starting at age 50:	
Focal occult blood test (FOBT)[a,b]	Annual
Flexible sigmoidoscopy	Every 5 years
FOBT + sigmoidoscopy	Annual and every 5 years
Colonoscopy	Every 10 years
Double contrast barium enema (DCBE)	Every 5 years

[a]US Preventive Service Task Force: annual or biennial.
[b]US Agency for Health Care Policy and Research: without rehydration.

High risk population

Individuals at increased risk for colorectal cancer are those with (1) a personal or family (first degree relative) history of colorectal cancer or adenoma, (2) longstanding ulcerative or Crohn's colitis, or (3) a genetic predisposition to a hereditary polyposis or non-polyposis syndrome. Individuals with a single first-degree relative with colorectal cancer have a risk of developing colorectal cancer approximately 2–3 times that of the general population[71,72]. In addition, cancers tend to occur at an earlier age in this population. If the first-degree relative was diagnosed with colon cancer at or before the age of 50 years, or if more than one relative is affected, the risk is 3–4 times that of the general population[74]. Individuals with first-degree relatives with adenomas have an approximately two-fold increased risk of colorectal cancer[72–74]. Patients with long-standing ulcerative colitis are at increased risk for colorectal cancer, particularly those with pancolitis and early age of onset of their disease[75]. Colorectal cancer in this group of patients is thought to develop in areas of mucosal dysplasia. Patients with longstanding Crohn's colitis have a similar increased risk of colorectal cancer[9]. Familial adenomatous polyposis coli (FAP) is a disease that results from inherited or acquired defects in

Table 2   Recommendations for colorectal cancer screening in individuals at increased risk

First-degree relative[a] with colorectal cancer or adenomatous polyp at age ≥60 years, or 2 second-degree relatives with colorectal cancer	Same as for average risk individual, but begin at age 40
Two or more first-degree relatives with colorectal cancer, or a single first-degree relative with colorectal cancer or adenomatous polyps diagnosed at age <60 years	Colonoscopy every 5 years, beginning at age 40 years or 10 years younger than the earliest colorectal cancer diagnosis in the family, whichever comes first
One second-degree[b] or any third-degree relative[c] with colorectal cancer	Same as for average risk individual
Family history of FAP[d]	Annual flexible sigmoidoscopy beginning at age 10–12 years if gene carrier or indeterminate[e]
Family history of HNPCC	Colonoscopy every 1–2 years, beginning at age 20–25 years, or 10 years younger than the earliest colorectal cancer diagnosis in the family, whichever comes first
History of inflammatory bowel disease (ulcerative colitis or Crohn's colitis)	Consider colonoscopy surveillance for dysplasia every 1–2 years beginning after 8 years of disease

[a]First-degree relatives include parents, siblings, and children.
[b]Second-degree relatives include grandparents, aunts, and uncles.
[c]Third-degree relatives include great-grandparents and cousins.
[d]Includes the subcategories of familial adenomatous polyposis, Gardner syndrome, some Turcot syndrome families, and AAPC.
[e]In AAPC, colonoscopy should be used instead of sigmoidoscopy because of the preponderance of proximal colonic adenomas. Colonoscopy screening in AAPC should probably begin in the late teens or early 20s.
Modified from Winawer *et al.* [9]. FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer.

the APC gene located on the fifth chromosome. Patients with this disease develop numerous polyps throughout the colon, which results in a 100% risk of colorectal cancer if the colon is not removed. Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder that results in a familial predisposition to multiple cancers. The colon cancers typically occur at a young age, are often located in the right colon, and may be associated with extracolonic neoplasms[76].

Screening recommendations (Table 2)

For individuals with a first-degree relative with a colorectal cancer or adenomatous polyp diagnosed at age ≥60 years or two second-degree relatives with colorectal cancer, the screening recommendations are the same as for the average risk population, except that screening should begin at age 40 (Patients with a personal history of colorectal cancer or adenomatous polyp are not included in this discussion, as they fall under the category of surveillance rather than screening). For individuals with two or more first-degree relatives with colon cancer, or a single first-degree relative with colon cancer or adenomatous polyp diagnosed before the age of 60 years, colonoscopy is recommended every 5 years, beginning at age 40 or 10 years earlier than the youngest age of colon cancer diagnosis in the family, whichever comes first. The recommendation for patients at risk for FAP is to receive genetic counseling (and possibly genetic testing to determine if the individual is a gene carrier) and to undergo flexible sigmoidoscopy annually beginning at age 10–12 years. Patients with a variant of FAP called attenuated APC (AAPC) have a tendency toward right-sided adenomatous polyps and

development of cancer approximately 10 years later than those with the usual form of FAP[77–80]. For this group, colonoscopy should be used rather than sigmoidoscopy, and screening should begin in the late teens or early 20s. The recommendation for patients with HNPCC is to receive genetic counseling (and possibly genetic testing) and to undergo colonoscopy every 1–2 years beginning at age 20–25 years, or 10 years earlier than the youngest age of colon cancer diagnosis in the family, whichever comes first. The recommendation for patients with longstanding ulcerative colitis and Crohn's colitis is to undergo colonoscopy with biopsies looking for dysplasia every 1–2 years beginning 8 years after diagnosis. One case-control study demonstrated reduced mortality from colorectal cancer among ulcerative colitis patients in colonoscopic surveillance programs[81].

New and emerging technologies

Computed tomographic colonography

Computed tomographic colonography (CTC) (also known as 'virtual colonoscopy') was introduced in 1994 as a non-invasive method of imaging the colon using helical CT[82]. Although CTC has been shown to be useful for certain clinical indications, it has not yet been endorsed as a colorectal cancer screening test and is not covered by most third-party payers when used for screening purposes. This examination is performed by acquiring a volumetric data set of the abdomen and pelvis with helical CT after insufflation of the colon with carbon dioxide or air. The colon can then be viewed with either 2-dimensional or 3-dimensional techniques. The 3-dimensional visualization technique provides a

perspective that simulates colonoscopic navigation of the colonic lumen.

Except for one study that was hampered by suboptimal technique and a steep learning curve[83], early CTC trials performed with single detector-row CT scanners demonstrated sensitivities of 68%–92% and specificities of 82%–98% for polyps ≥1 cm[84–90]. A meta-analysis of these early trials confirmed reasonably high pooled sensitivities by patient and by lesion of 88% and 81%, respectively, with a pooled specificity of 95% for polyps ≥1 cm[91]. More recent studies performed with 4-detector row scanners have demonstrated sensitivities and specificities of 82%–100% and 90%–98%, respectively for polyps ≥1 cm[92–95]. It is important to recognize, however, that these trials were not performed on screening populations but on individuals who were at increased risk for colorectal neoplasia. A large single institution screening trial using single detector-row CT demonstrated individual reader sensitivities of 59%–73% and specificities of 95%–98% for polyps ≥1 cm[59]. A smaller single institution screening trial using multidetector-row CT demonstrated a sensitivity of 100% for polyps ≥1 cm, but in that study only three patients had polyps of that size[96].

One large multicenter trial comparing multidetector-row CTC and fiberoptic colonoscopy for detecting polyps in patients undergoing colorectal cancer screening has been published[55]. In that study, the sensitivities of CTC and colonoscopy for adenomatous polyps ≥1 cm were 94% and 88%, respectively. Thus, in that trial, CTC outperformed optical colonoscopy. However, two multicenter trials in which patients with clinical indications for colonoscopy were evaluated with CTC showed sensitivities for polyps ≥1 cm of only 55% and 59%[61,97]. One of these latter studies[97] suffered from inadequate reader training and both used technology that was somewhat outdated.

CTC has a number of potential advantages compared with conventional fiberoptic colonoscopy. It is a non-invasive technique, requires no sedation, can be completed in a much shorter time, and is associated with a lower risk of complications. The only study of morbidity related to CTC reported to date has demonstrated a perforation rate of 3 in 7180 studies (0.04%)[98]. No deaths related to CTC have been reported. In addition, CTC has the potential to eliminate some of the blind spots that can be problematic with conventional colonoscopy. Moreover, because the CTC examination is not limited to the colon, it is capable of demonstrating clinically important extracolonic abnormalities[99–103]. An additional potential advantage of CT colonography is the possibility of avoiding rigorous bowel preparation through the use of stool and fluid tagging. A study of CTC without cathartic preparation in over 200 patients demonstrated a sensitivity of 95.5% for polyps 8 mm and larger[104].

On the other hand, CTC has some disadvantages compared to colonoscopy. CTC does not allow biopsy or removal of polyps that are identified, and it requires the use of ionizing radiation. In addition, the sensitivity of CTC for detecting clinically significant polyps has varied considerably in the clinical trials published to date.

Immunochemical FOBT

Immunochemical fecal occult blood tests use monoclonal and/or polyclonal antibodies that detect the intact globin protein portion of human hemoglobin[105]. Whereas guaiac-based tests can yield false-positive results if certain foods (meats, some raw fruits and vegetables), vitamins (vitamin C or high levels of foods containing vitamin C) or drugs (aspirin) are ingested in the days before taking the test[19–21], immunochemical FOBTs do not react with non-human hemoglobin or with uncooked fruits or vegetables that may contain peroxidase activity. Thus, immunochemical FOBT has the potential not only to improve specificity, but possibly to increase patient compliance because of the lack of dietary restrictions. In addition, because globin does not survive passage through the upper gastrointestinal tract, the test is specific for bleeding in the colon and rectum[106]. Nevertheless, immunochemical FOBT has limitations similar to guaiac-based FOBT related to the intermittency of bleeding from colorectal adenomas and cancers.

Fecal DNA

DNA is shed continuously from the gastrointestinal tract, is stable in stool, and can be detected in minute amounts through use of amplification tests, such as polymerase chain reaction[107]. Because many DNA mutations associated with colorectal carcinogenesis have been characterized, identification within stool of DNA containing these mutations may be a way of identifying individuals with pre-clinical and clinical disease[105]. Studies of fecal DNA testing in patients with advanced, symptomatic colorectal lesions have reported sensitivities of 62%–91% for cancer and 27%–82% for advanced adenomas[108–112]. However, a large-scale multi-center study involving asymptomatic, average risk individuals showed that although fecal DNA testing was more sensitive than guaiac-based FOBT, it detected only 18% of subjects with advanced neoplasia and only 52% of those with invasive carcinoma[113]. Thus, further marker discovery and technological refinements will be necessary to improve test performance[114]. Nevertheless, stool-based molecular approaches to colorectal cancer screening hold great promise.

Video capsule endoscopy

The capsule video endoscope is a pill that contains a camera and is small enough to be swallowed. Developed

by an Israeli company (Given Imaging Ltd.), the capsule records multiple images per second as it passes through the gastrointestinal tract[115]. The images are recorded on a portable data recorder worn on a belt and are reviewed as a video. Clinical studies of this device thus far have been limited to the stomach and small bowel. Extending the capsule endoscopy examination to the colon would require that the capsule have a longer battery life[115]. In addition, a formal cathartic bowel preparation as for colonoscopy would be required.

Conclusion

Although colorectal cancer screening has been shown to reduce mortality from colorectal cancer, patient compliance with screening recommendations remains poor. Obstacles to colorectal cancer screening compliance include the inconvenience, invasiveness and unpleasantness of some of the tests and their preparations. Newer technologies such as stool-based DNA analysis and computed tomographic colonography ('virtual colonoscopy') hold great promise not only for improving detection of colorectal cancer and adenomatous polyps but also for improving compliance with colorectal cancer screening recommendations.

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