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Colon cancer screening

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Colorectal cancer is a major health problem worldwide. Last year in the United States alone, more than 130 000 people were diagnosed with colorectal cancer and more than 56 000 died of their disease[1]. Fortunately, this neoplasm is highly suited to screening because of its long preclinical phase, during which it is detectable and curable[2]. Nevertheless, screening programs for colorectal cancer have been only partly successful, owing largely to poor patient compliance with screening recommendations[3,4]. A number of organizations including the World Health Organization (WHO), the American Cancer Society (ACS), the Agency for Health Care Policy and Research (AHCPR), the US Preventive Service Task Force (USPSTF), and the American Gastroenterology Association (AGA) have issued or endorsed guidelines for colorectal cancer screening. 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, and outlines the currently recommended guidelines for screening based on risk category.

Average-risk population

Average-risk patients are asymptomatic individuals aged 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 two most recently published screening recommendations, those of the ACS[5] and AHCPR[6], present guidelines for screening average-risk patients in the form of lists of options (Table 1). The options include annual fecal occult blood test (not included as a stand alone test in the ACS guidelines), flexible sigmoidoscopy every 5 years, annual fecal occult blood test plus flexible sigmoidoscopy every 5 years, double-contrast barium enema every 5 to 10 years, and colonoscopy every 10 years.

Table 1 Recommended options for colorectal cancer screening in asymptomatic, average-risk individuals*

Starting at age 50
Annual FOBT†
Flexible sigmoidoscopy every 5 years
Annual FOBT and sigmoidoscopy every 5 years
Colonoscopy every 10 years
Double-contrast barium enema every 5–10 years

*Winawer SJ, Fletcher RH, Miller L *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594–642.
†The American Cancer Society does not recommend fecal occult blood testing (FOBT) by itself.

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 FOBT in reducing colorectal cancer mortality by 15% to 33%[7–9]. 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. 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[10]. Limitations of FOBT include its relatively low sensitivity for detecting cancers and its inability to detect the vast majority of adenomas[11]. Because colorectal cancers bleed intermittently, 50% or more of patients with colorectal cancer may have a negative test result[11,12]. Thus, to be effective, FOBT must be administered annually or biennially, which makes patient compliance a problem. Furthermore, the positive predictive value of FOBT is only approximately 10%[11,12].

Flexible sigmoidoscopy

Data from two case–control studies support the effectiveness of flexible sigmoidoscopy in reducing colorectal cancer mortality[13,14]. Individuals in these studies who had undergone at least one screening sigmoidoscopy during the previous 10 years had only a 21% to 30% risk of developing fatal colorectal cancer as control subjects. Compared with colonoscopy, flexible sigmoidoscopy is less expensive and has a lower complication rate (approximately one to two perforations per 10 000 examinations)[6,15]. 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[16,17]. If a polyp is detected by sigmoidoscopy, colonoscopy is still needed to evaluate the entire colon.

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. Nevertheless, there is little direct evidence to support such a combined approach. Furthermore, a large number of colonic adenomas and carcinomas are not within 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[18–22].

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 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[15] and uncontrolled observational studies[23–25]. The case–control study showed a 40% to 50% reduction in colorectal cancer incidence in individuals who had undergone colonoscopy or polypectomy[15]. A limitation of colonoscopy is that it is incomplete in 5–15% of patients[18,19,26]. In addition, colonoscopy is associated with the highest risk of complications of all screening tests. Perforation occurs in approximately 1 in 1000 colonoscopies, major bleeding occurs in approximately 3 per 1000, and one to three patients undergoing colonoscopy die of complications from the procedure[6,19,26–28].

Barium enema examination

Because of its higher sensitivity than single contrast barium enema, double-contrast barium enema is considered the current 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[29–31]. No data are available on the sensitivity of double-contrast barium enema in a screening population. In patients undergoing diagnostic examinations, the reported sensitivity of this test for the detection of cancer is 85–90%[32–34], and the sensitivity for adenomas larger than 1 cm is 75–90%[35,36]. However, recently published data from the National Polyp Study in the United States demonstrated a sensitivity for double-contrast barium enema of only approximately 50% for polyps 1 cm or larger in patients undergoing surveillance after removal of adenomatous polyps[37]. Advantages of double-contrast barium enema compared with colonoscopy are that it is safer (approximately one perforation in 25 000 procedures)[38], less expensive, and does not require sedation. Its major disadvantages are its lower sensitivity and the inability to remove polyps, thus requiring colonoscopy or sigmoidoscopy after positive examinations.

Computed tomography (CT) colonography

CT colonography (also known as 'virtual colonoscopy') is a relatively new radiologic procedure that holds promise as a colorectal cancer-screening test, but requires further evaluation. In this study a helically acquired volumetric data set of the abdomen and pelvis is obtained after insufflation of the colon with air or carbon dioxide. 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. Prospective studies performed in selected groups of high-risk patients have reported sensitivities with CT colonography of 50% to 91% for polyps 1 cm or larger[39–43]. It is important to note, however, that the results of such studies cannot be generalized to a screening population of average-risk individuals. One potential advantage of CT colonography is the possibility of avoiding rigorous bowel preparation through the use of barium stool tagging and electronic subtraction of stool from the colon prior to diagnostic evaluation of the images[44]. Whether CT colonography will become a viable alternative to colonoscopy for colorectal cancer screening remains to be seen.

Cost-effectiveness

Most studies of the cost-effectiveness of FOBT (every 1 to 2 years), flexible sigmoidoscopy (every 5 years), colonoscopy (every 10 years) and double-contrast barium enema examination (every 5 to 10 years) have

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

First-degree relative with colorectal cancer or adenomatous polyp(s): same as for average risk individual, but begin at age 40
Family history of FAP Genetic counseling (consider genetic testing) Annual flexible sigmoidoscopy beginning at puberty if gene carrier or indeterminate
Family history of HNPCC Genetic counseling (consider genetic testing) Colonoscopy every 1–2 years beginning at age 20–30, annually beginning at age 40
History of inflammatory bowel disease Consider colonoscopy surveillance for dysplasia every 1–2 years beginning after 8 years of disease for pancolitis and after 15 years of disease for left-sided colitis

*Winawer SJ, Fletcher RH, Miller L *et al*. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594–642.
FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.

shown costs per life-year saved ranging from approximately $2000 to $15 000 for FOBT up to $22 000 for colonoscopy[45–48]. 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 to $50 000[49–50].

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 double-contrast barium enema examination), flexible sigmoidoscopy every 5 years (followed by colonoscopy if adenomatous polyp or cancer found), annual FOBT and sigmoidoscopy every 5 years, colonoscopy every 10 years, or double-contrast barium enema examination every 5–10 years. It should be noted that the American Cancer Society does not endorse the option of FOBT by itself because of the relatively low mortality reductions that have been associated with its use[5].

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 nonpolyposis syndrome. Individuals with a single first-degree relative with colorectal cancer have a risk of developing colorectal cancer approximately 1.7 times that of the general population[51]. In addition, cancers tend to occur at an earlier age in this population. First-degree relatives of patients with adenomas have a similar increased risk of colorectal cancer[52,53]. 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[54]. Colorectal cancer in this group of patients is thought to develop in areas of mucosal dysplasia. Patients with longstanding Crohn's colitis are also at increased risk for colorectal cancer, but the risk is lower than that associated with ulcerative colitis[55]. Familial adenomatous polyposis coli (FAP) is a disease that results from inherited or acquired defects in 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 nonpolyposis 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[56].

Screening recommendations (Table 2)

For individuals with first-degree relatives with colorectal cancer or an adenomatous polyp, 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.) The recommendation for patients with FAP is to receive genetic counseling (and possibly genetic testing to determine if the patient is a gene carrier) and to undergo flexible sigmoidoscopy annually beginning at puberty. 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 20–30, with annual colonoscopies beginning at age 40. The recommendation for patients with longstanding ulcerative colitis is to undergo colonoscopy with biopsies looking for dysplasia every 1–2 years beginning 8 years after diagnosis for pancolitis and beginning 15 years after diagnosis for left-sided disease. However, there is no direct evidence that this practice reduces colorectal cancer mortality in these patients and none that it is more effective than colectomy based on extent and duration of disease[6]. Surveillance for colorectal cancer is not currently recommended for patients with Crohn's colitis[57].

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Ovarian cancer screening

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Introduction

Ovarian cancer is the most common gynaecological malignancy in the developed world. It also carries the worst prognosis with an overall 5-year survival of 30%. This is likely to be due to the disease frequently presenting late, the ovary position within the peritoneal cavity resulting in minimal local irritation, or interference with vital structures until ovarian enlargement is considerable, or metastasis occurs. Seventy per cent of women are diagnosed with stage III or IV disease, with 5-year survivals of 15–20% and less than 5%, respectively[1]. Despite an increase in understanding of the molecular events underlying malignancy, and advances in both surgery and chemotherapy, the overall prognosis of ovarian cancer has changed little over the last 30 years. However, women who are diagnosed at an early stage do have a significantly improved prognosis, with survival of above 80% in stage I disease, and above 90% in those diagnosed at stage Ia[2]. The best way of improving outcome may be, therefore, to detect the condition at an early stage, when the prognosis remains relatively good, via a screening programme. This is an exciting prospect and screening trials have shown some encouraging results. However, as yet screening has not been shown conclusively to reduce mortality from ovarian cancer. In addition, our lack of knowledge about disease progression and of primary peritoneal cancer, as well as the possible surgical and psychological morbidity that may result from screening, should be considered. There are also, of course, cost implications.

What to screen for

A screening programme should ideally be based on the detection of a pre-malignant condition in order to lower disease incidence and maximize mortality reduction, as is the case with the cervical screening programme. Although it is suggested that inclusion cysts and benign and borderline ovarian tumours may be pre-malignant, this remains speculative. Crayford *et al*. recently analysed follow-up data from an ovarian cancer screening trial to assess whether removal of persistent ovarian cysts was associated with a reduction in mortality from ovarian cancer[3]. No such reduction was found relative to other cancers, although it is difficult to interpret the findings in the absence of a control group, and incidence may have been a more appropriate end-point than mortality. In the absence of confirmed pre-malignant change, screening for ovarian cancer is directed at present to the detection of pre-clinical disease.

What is required from a screening test

A suitable screening test requires both high sensitivity and specificity. Women who have a positive screen require further investigation, often in the form of exploratory surgery. It is therefore imperative to maximize specificity in order to obtain a high positive predictive value, and decrease the number of false-positive screens. In the general population, a specificity of 99.6% is required to achieve a positive predictive value of 10%[4], i.e. to limit the number of unnecessary surgical