Review Article

Colorectal Cancer Screening

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Article info

Abstract

Colorectal cancer (CRC) was the third-leading cause of cancer death in Taiwan in 2008. The natural history of CRC provides a chance for screening and prevention. Most CRC develops from adenomatous polyps. This progression takes at least 10 years in most people. About 90% of CRC develops after 50 years of age. Screening tests can identify cancers, usually at an early stage, and polyps, which can be removed before malignant change. Removal of adenomatous polyps can reduce the risk of developing CRC by up to 90%. Several factors increase the risk of CRC: a familial history of colon adenomas, CRC, familial adenomatous polyposis, or hereditary nonpolyposis colon cancer; a personal history of treated CRC or adenoma, or ulcerative pancolitis for more than 10 years; old age; a diet high in fat and red meat and low in fiber; a sedentary lifestyle; and cigarette smoking. Colonoscopy is the best screening method, and detects most small polyps and almost all large polyps and cancers. Polyps can be removed during colonoscopy. The risk of serious bleeding or perforation is about 1/1000. In the future, computed tomography colonography may become a good screening tool. The double contrast barium enema has largely been replaced by other screening methods. Combined screening with a fecal occult blood test and sigmoidoscopy is a possible option. People with an average risk of CRC should begin screening at 50 years of age. Colonoscopy is recommended every 10 years or computed tomography colonography, sigmoidoscopy, or a double contrast barium enema every 5 years. Stool testing once per year is another alternative. Patients with an elevated risk should be screened with colonoscopy, usually beginning at 40 years of age. Screening for family members of those with familial adenomatous polyposis and hereditary nonpolyposis colon cancer should be more intense and be initiated at 20 years of age. If polyps are found and removed during a screening colonoscopy, a surveillance colonoscopy should be done 1–5 years later, according to the size and histology of the removed adenoma. [*Tzu Chi Med J* 2009;21(3):190–196]

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1.   Introduction

Colorectal cancer (CRC) is the third most prevalent form of cancer and the second leading cause of cancer death in the United States [1,2]. It accounts for up to 9% of cancer deaths overall. Up to one third of people with CRC will ultimately die of it. The lifetime incidence of CRC for an average-risk person is about 5%. The incidence rate of CRC in the United States has been declining, partly because of screening. The screening rate for CRC in adults over 50 years of age has increased recently. The rate was 60.8% in 2006, but this is not thought to be satisfactory [3–5]. In contrast, the incidence rate of CRC in Taiwan is rising, probably because of behavior changes and the different screening policy [6]. It was the third leading cause of cancer death in Taiwan in 2008 (Fig. 1). The lifestyle in Taiwan has become more and more westernized in the past few decades. The practice of screening fecal occult blood tests for people over 50 years old started only several years ago.

Prevention of CRC is feasible, as demonstrated by several facts. First, CRC is rare before the age of 40 years; around 90% of cases occur after the age of 50 years [1]. The incidence rate rises with increasing age, and reaches 3.7/1000/year by the age of 80 years [1]. Second, most cases of CRC develop from an adenoma. A sequence of small adenoma to large adenoma to dysplasia and then to cancer is suggested [7]. Third, the development of adenoma from normal mucosa may take more than 10 years, and the development of cancer from adenoma may take 2–30 years [8]. Because of the slow progression rate from normal mucosa to adenoma, and to cancer, CRC can be prevented if adenomas are found and removed before malignant transformation (Fig. 2). The National Polyp Study Work Group reported that in a group of 1418 patients whose adenomas were removed and were

followed for an average of 6 years, the incidence of CRC decreased by 88–90% compared with that in patients whose adenomas were not removed, and by 76% compared with that in the general population [9].

2.   Screening recommendations according to risk level

Fig. 3 shows an algorithm for the screening policy recommended by the American Cancer Society and the United States Multi-Society Task Force on Colorectal Cancer, which was updated in 2008 [10]. Patients with
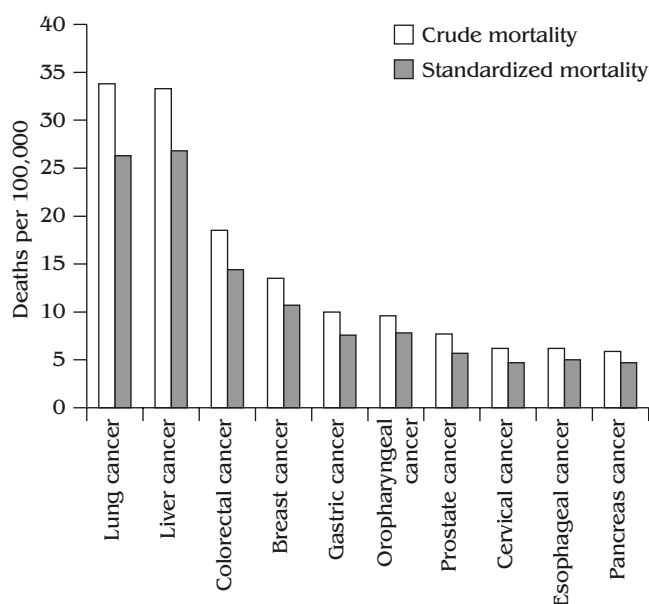
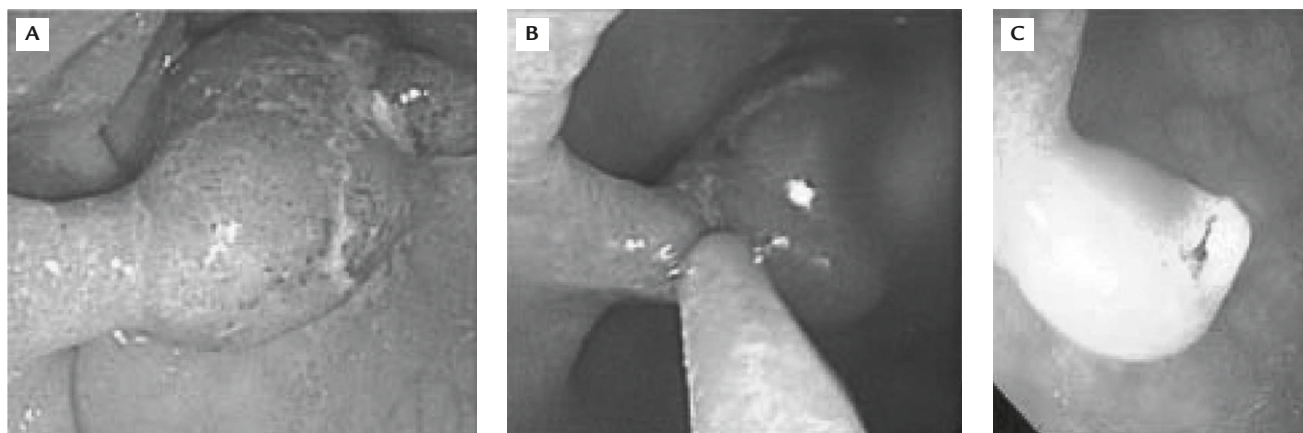**Fig. 1 — Leading causes of cancer death in Taiwan 2008. Data taken from Reference 6.**

Fig. 2 — (A) Pedunculated polyp in the sigmoid colon of a patient seen on screening colonoscopy performed in our hospital. (B) The polyp was grasped by a snare. (C) It was then cut off with an electric current.
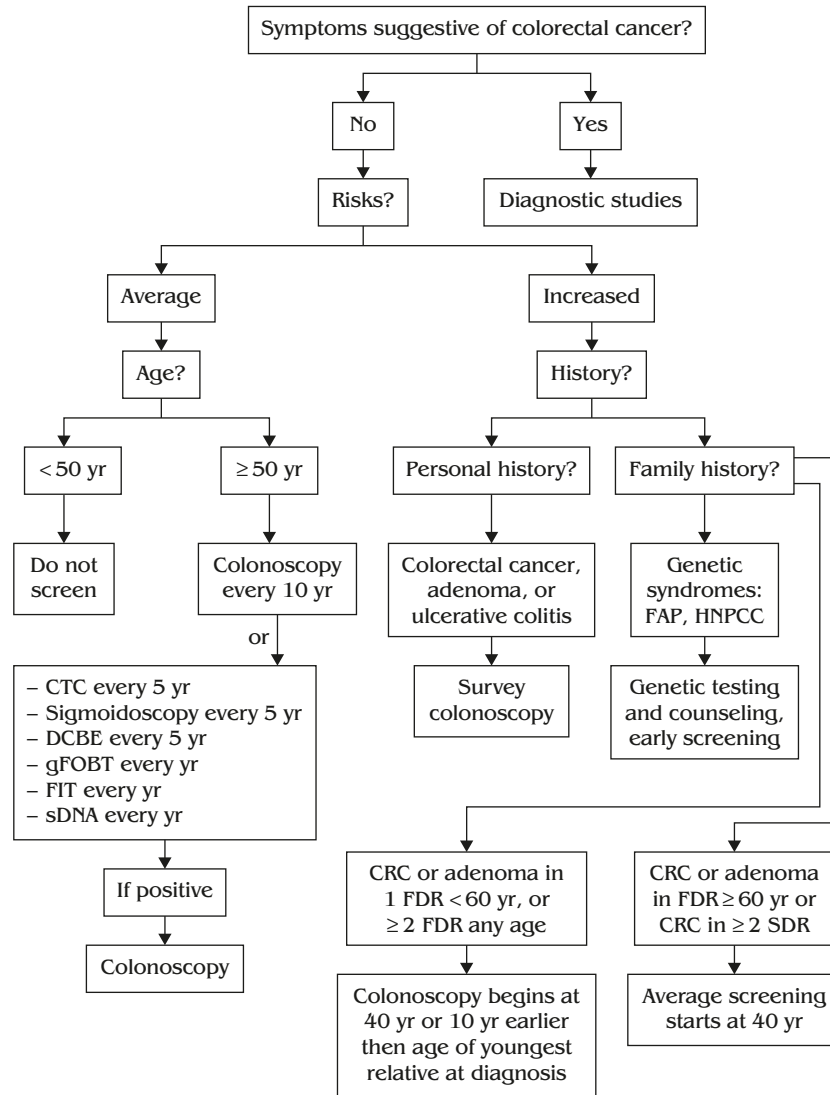
Fig. 3 — Algorithm of the guidelines recommended by the American Cancer Society and the United States Multi-Society Task Force on Colorectal Cancer. CTC=computed tomography colonography; DCBE=double-contrast barium enema; gFOBT=guaiac-based fecal occult blood test; FIT=fecal immunological test; sDNA=stool DNA panel test; FAP=familial adenomatous polyposis syndrome; HNPCC=hereditary nonpolyposis colon cancer syndrome; CRC=colorectal cancer; FDR=first-degree relatives; SDR=second-degree relatives. Modified from Reference 10.

symptoms suspected to indicate CRC are advised to undergo a diagnostic work-up without delay. For asymptomatic patients, the screening policy depends on specific age and risk level.

The risk level should be determined by the personal and familial history of CRC and adenomas, starting at the age of 20 years, with reassessment every 5 years. The risk level is high for patients who have been treated for CRC previously, up to a three-fold increased risk of CRC compared with the general population [11]. Patients who had colorectal adenomas removed previously also have an increased risk of CRC [12]. They should be followed with colonoscopy (the nature of follow-up depends on the nature of the removed

adenomas, as will be discussed later). Patients with ulcerative pancolitis for more than 8–10 years should be surveyed with colonoscopy every year with segmental random biopsies.

Family members of patients with familial adenomatous polyposis syndrome have hundreds to thousands of polyps throughout the colon beginning in adolescence [13]. All family members should have genetic counseling and genetic testing when available. A screening sigmoidoscopy or colonoscopy should be conducted before the age of 20 years. Total colon colectomy is advised if the patient is confirmed to harbor the adenomatous polyposis coli gene, because CRC will develop in nearly 100% of these cases before

the age of 50 years. Hereditary nonpolyposis colon cancer is a syndrome characterized by proximal colon cancers (and other cancers including endometrium, stomach, ovary, pancreas, ureter and kidney, biliary tract, and brain) in relatively young members of a family [14]. It should be suspected if more than one family member had hereditary nonpolyposis colon cancer-related cancer at a young age (between 30 and 40 years of age). Genetic counseling and testing for DNA mismatch repair genes are suggested. Colonoscopy screening should be started at the age of 30 or 40 years.

The risk of CRC is increased in family members of patients with CRC or colorectal adenoma [15–17]. Persons with one first-degree relative who had CRC diagnosed before the age of 60 years, or two or more first-degree relatives who had CRC or adenoma at any age, should have a colonoscopy screening starting at the age of 40 years, or 10 years earlier than the age at diagnosis of the youngest index case—whichever is earlier. Persons with one first-degree relative who had CRC or adenoma diagnosed after the age of 60 years, or two or more second-degree relatives with CRC, should have screening tests on the same schedule as average-risk persons, but starting at the age of 40 years.

Several risk factors for CRC have been suggested by observational studies (Table 1) [18], but they do not require changes in screening recommendations.

Table 1 — Factors associated with an increased and decreased risk of colorectal cancer

Increased risk	Decreased risk
Consumption of red meat	Consumption of vegetables, fruits, and fiber
Lack of physical activity	Multivitamins (with folic acid)
Obesity	Postmenopausal hormone use
Cigarette smoking	Calcium supplementation
Alcohol use	Selenium
	Aspirin and other nonsteroidal anti-inflammatory drugs
Modified from Reference 18.	

3.   Screening methods

Besides colonoscopy, several methods have been recommended for CRC screening. These include the guaiac-based fecal occult blood test, immunological fecal occult blood test, stool DNA test, flexible sigmoidoscopy, double-contrast barium enema (DCBE), and computed tomography (CT) colonography. Factors to be considered in the choice of a screening test are listed in Table 2 [8]. No single test is superior to the others. Patient preference should also be considered. An annual immunological fecal occult blood test (iFOBT) for people aged 50 years or more, and a colonoscopy if the iFOBT is positive, is the current screening policy for CRC recommended by the Department of Health in Taiwan.

The guaiac-based fecal occult blood test (gFOBT) is based on a peroxidase reaction by heme, which transforms guaiac into a blue color. It can be affected by certain components of food. Patients should eat a high fiber diet for 2 days with no red meat, vitamin C, or gastric irritant drugs. Three stool samples should be obtained. It has been shown that biennial gFOBT tests can reduce CRC mortality by up to 30% after 13 years [19]. Slightly lower mortality reductions (13–18%) have been reported in other trials [20–23]. Theoretically, FOBT cannot detect most adenomas, because adenomas seldom bleed unless they are large. The test results in many false positives, leading to many unnecessary colonoscopies. The need for a restricted diet for gFOBT decreases screening compliance. An annual gFOBT remains one of the recommended screening methods for CRC, but it is gradually being replaced by iFOBT.

iFOBT is based on immunological detection of human (hemo-) globin in stool, and does not detect upper gastrointestinal bleeding (globin is digested) or food peroxidase (including animal globin). It requires only one stool sample and no diet restriction. It is more expensive than gFOBT. The sensitivity and specificity for CRC and adenoma detection with iFOBT are higher than those of gFOBT [24–26]. The new quantitative iFOBT [27] has shown even better performance, with a sensitivity and specificity of 94% and 87%

Table 2 — Summary of the characteristics of screening tests for colorectal cancer and adenomas

	For cancer	For polyps	Complexity	Effect	Evidence	Risk
gFOBT	+	+	+	+	+++	−
iFOBT	+	+	+	++	+	−
Sigmoidoscopy	++	+++	++	+++	++	++
DCBE	++	++	+++	++++	+	++
Colonoscopy	++++	+++++	++++	+++++	+	+++
CTC	+++	++++	+++	++++	+	+
sDNA	++	++	++	++	+	−

gFOBT = guaiac-based fecal occult blood test; iFOBT = immunological fecal occult blood test; DCBE = double-contrast barium enema; CTC = computed tomography colonography; sDNA = stool DNA panel test. Modified from Reference 8.

for CRC and 67% and 91% for advanced adenoma, respectively. The quantitative iFOBT is used for mass screening of CRC in the general population by the Department of Health in Taiwan.

A panel of DNA markers in stool samples has been used to screen for CRC (28,29). The sensitivity for detecting CRC ranged from 20% to 71%, with a specificity of around 82–96%. However, it misses many cancers and advanced adenomas detected by colonoscopy. The test is not cost effective at present.

Persons having a DCBE must undergo bowel preparation to visualize the entire bowel and the test is relatively safe. It can detect most CRCs and about half of large (> 1 cm) polyps (30). Any DCBE abnormalities must be confirmed by colonoscopy. It can miss up to 20% of CRC (31). False-positive findings due to stool or air are common. The radiation dose is also a concern. The use of DCBE has been declining. The procedure might therefore be limited by insufficient training of technicians and radiologists. It may be of value where colonoscopy resources are limited.

Sigmoidoscopy refers to the use of a 60-cm flexible endoscope. Around two-thirds of CRC and adenoma occur in the distal 60 cm of the large bowel (32). The patient needs minimal preparation and it can be done anytime in the office of a family doctor or an endoscopist. The procedure is considered inadequate if the scope cannot observe at least 40 cm in depth. The most serious complication of sigmoidoscopy is perforation, which occurs in around 0.88 per 1000 procedures (33). Case-control studies have shown that sigmoidoscopy reduces CRC mortality by up to one third (34–36). A surveillance colonoscopy should follow a positive sigmoidoscopy.

Colonoscopy gives a direct view of the mucosa, and biopsy of cancer and removal of most adenomas can be completed during the same procedure. Removal of polyps can prevent CRC (9). There are no randomized controlled studies showing that colonoscopy reduces CRC mortality in persons of average risk. The rate of perforation or major bleeding is about 1 in 1000 colonoscopies (33,37). Colonoscopy requires vigorous bowel preparation, is rather uncomfortable for most patients, may require conscious sedation, and requires the patient to be accompanied after the procedure. The sensitivity is operator-dependent. The detection rates for neoplasms are higher if the withdrawal-observation time is 6 minutes or longer (38). In one study, the overall miss rate for polyps was 22%: 2% for adenomas 10 mm or larger, and 25% for adenomas smaller than 5 mm (39).

CT colonography (formerly known as virtual colonoscopy) requires bowel preparation in a similar way to colonoscopy. The technique is gradually improving and with it the sensitivity and specificity for CRC and adenoma detection (40). Colonoscopy is needed following a positive CT colonography finding. Radiation exposure is a concern. Extracolonic lesions may be found incidentally, which may cause undue anxiety. Sensitivity for large adenomas is good but flat or depressed adenomas may easily be missed. As the procedure becomes more sophisticated, it may replace colonoscopy as a first-line screening tool (41).

Some colon cancers arise from nonpolypoid (flat or depressed) lesions which are difficult to identify even with colonoscopy; careful observation and often special stains are needed. Nonpolypoid adenomas may be more likely to have dysplasia or cancer than polypoid ones of the same sizes (42–44). These may account for up to one third of all adenomas and can only be detected by colonoscopy. For this reason, colonoscopy remains the gold standard for CRC detection.

4. Surveillance colonoscopy

Once polyps are found, they should be completely removed. If severe dysplasia or carcinoma *in situ* is found, the resection margin should be free of any suspicious invasion. If there is doubt, colonoscopy should be repeated to see if any residual lesions remain, and these should be excised as completely as possible. If the malignant portion is poorly differentiated, there is vascular or lymphatic invasion, or the resection margin is not free, further evaluation with CT or positron emission tomography and surgical intervention should be considered.

After the complete removal of polyps, patients should be followed with surveillance colonoscopy. The interval of surveillance colonoscopy depends on the nature and number of polyps found. The histology of polyps can be roughly classified into either hyperplastic or adenomatous polyps. Although hyperplastic polyps have a characteristic appearance, biopsy is required for diagnosis. Hyperplastic polyps have a low risk of malignant change except in the unusual case of hyperplastic polyposis syndrome (45). Around two thirds of polyps are adenomatous. Adenomas are found in up to 25% of persons aged 50 years, and in up to 50% of persons up to the age of 70 years (46). The risk of CRC increases with the size, number, and aggressive histology (villous *vs.* tubular, and grade of dysplasia) of adenomas (47,48). Larger adenomas are more likely to have a villous component and dysplasia. Lesions with a villous histology are more prone to malignant change. Higher grades of dysplasia reflect a higher likelihood of change and more rapid malignant change. The recommended surveillance intervals suggested by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society (47) are summarized in Fig. 4.

The effectiveness of colonoscopy in preventing CRC depends on the detection and removal of adenomas.
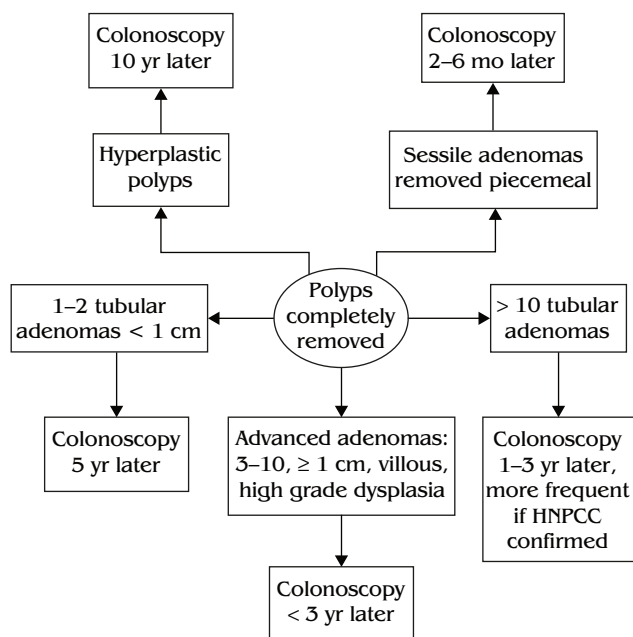
Fig. 4 — Algorithm of guidelines for colonoscopy surveillance after polypectomy. HNPCC=hereditary nonpolyposis colon cancer. Modified from Reference 47.

This in turn depends on the adequacy of bowel preparation and careful mucosal visualization. The term "interval cancer" refers to CRC found within 5 years of a completely negative colonoscopy. Interval cancer accounts for about 5% of registered CRCs (49,50). Research has shown that endoscopists who had longer mean times for withdrawal of the colonoscope had greater rates of adenoma detection (51). The endoscopist should look carefully behind folds, efface mucosa where feces or bubbles interfere with viewing, dedicate sufficient time, and avoid fatigue during examination.

5. Summary

CRC is both common and lethal. However, it is preventable, principally because of its slow development and transformation from adenoma to carcinoma, occurring mostly after the age of 50 years. Screening is recommended starting from the age of 50 years for people of average risk. People with increased risk should be screened earlier, as depicted in Fig. 3. There are several methods suggested for CRC screening. At present, the iFOBT is provided free by the Department of Health in Taiwan. Colonoscopy is the gold standard for CRC detection, provided that the procedure is performed adequately. Surveillance colonoscopy is recommended after the complete removal of adenomas, as recommended in Fig. 4. However, it should

be stressed that recommendations are for screening asymptomatic people. One should suggest colonoscopy directly when a patient is symptomatic.

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