An Overview of Colorectal Cancer Screening

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Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women. It is the second leading cause of cancer death for men and women combined. About 93,090 cases of colon and 39,610 rectal cancers are thought to be diagnosed in 2015. It has been estimated that about 49,700 deaths will be from CRC in 2015.

Risk factors associated with CRC include history of inflammatory bowel disease (i.e., Crohn’s disease or ulcerative colitis), diabetes mellitus type II, obesity, lack of physical activity, increasing age, moderate to heavy alcohol use, smoking, large consumption of red meat, decreased calcium intake, and decreased intake of fibre, fruits and vegetables. Family history or personal history of CRC and polyps is another important risk factor. There are also certain genetic conditions such as Lynch syndrome also known as hereditary nonpolyposis colorectal cancer (HNPPC) along with familial adenomatous polyposis that are associated with an increased risk of CRC [1].

Screening and removal of premalignant adenomas can reduce the incidence of cancer and cancer deaths. CRC usually arises from colorectal adenomas which progress from early to advanced to invasive cancer. A German epidemiological study showed that advanced adenomas progress to CRC and strongly increases with age. For women, in the age group of 55-59 the transition rate of adenomas to CRC of 2.6% increases to 5.6% in the age group of women greater than 80. For men, the annual transition rate from advanced adenoma to CRC increases from 2.6% in age group 55-59 to 5.1% in men greater than the age of 80 [2].

Over the years, incidence rates for CRC have been decreasing. From 2007 to 2011, incidence rates have decreased by 4.3% per year for those above the age of 50. Incidence rates have increased by 1.8% for adults younger than 50 years of age. The overall death rate has decreased by 2.5% per year during this time period. It seems as though these declining incidences rates are likely due to more knowledge about the risk factors associated with CRC along with improvements in screening [1].

There are many options available for screening to prevent CRC. In this review, we will discuss various strategies for screening CRC from noninvasive blood tests to endoscopy to different imaging modalities.

Fecal Occult Blood Test (FOBT)

There are two commonly used types of stool blood tests: guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT). Fecal occult blood tests (FOBT) rely on the presence of a bleeding CRC or an adenoma. gFOBT detects blood in the stool through the activation of peroxidase activity. Generally for the gFOBT there are three collections of the sample from consecutive bowel movements at home. Collection of three samples helps increase sensitivity of the test [3,4].

Advantages of this test include that the test can be easily performed at home without any serious complications. If a positive test result were to occur, patient would need to have a colonoscopy. The sensitivity is variable for CRC screening with reported figures varying from about 13 to 64% and about 11 to 41% for advanced adenomas. Specificity for CRC screening is high and ranges from about 91 to 95% [6-9]. A Cochrane review consisting of more than 320,000 people demonstrated that participants allocated to screening had a 16% reduction in the relative risk of death from CRC, or 0.1 to 0.2 fewer colorectal cancer deaths per 1,000 patient-years [6,10].

Immunochromic Fecal Occult Blood Tests (FIT)

FIT is able to detect human globin in stool by means of an immunochromic reaction. FIT is able to quantify actual hemoglobin concentration in stool [9,11,12]. In comparison to gFOBT, FIT does not have any dietary restrictions. In addition, there is no need to stop anticoagulants or aspirin prior to this test. The test is processed in an automated lab and only one measurement is needed versus three samples which are needed with the gFOBT.

Studies have shown that the sensitivity of FIT ranges from 47.1 to 100% and the specificity ranges from 88.2 to 97.1% [13-21]. In two Dutch population-based studies it was found that FIT detected advanced neoplasias three times more frequently than gFOBT [22,23]. It was seen that with gFOBT there were 6 subjects with advanced neoplasias per 1,000 screened whereas FIT, when using a cut-off of 50ng hemoglobin per milliliter found 21 subjects per 1,000 screened. The study also showed that the distribution between true positives and false positives was the same with FIT and gFOBT [24].

In a Japanese study consisting of 22,666 participants who underwent colonoscopy and FIT it was found that neoplasia was seen in 36.5% (449 of 1237) of the FOBT positive patients and in 18.8% (3876 of 20,574) of the FOBT negative patients. This demonstrated that patients with a positive FIT had an increased risk for neoplasia as opposed to those with a negative FIT (relative risk, 1.9; 95% confidence interval, 1.8-2.1). The study showed that the sensitivity of FIT was 27.1% for advanced neoplasia and 65.8% for cancer. FIT was also found to be less sensitive at detecting advanced neoplasia located in the proximal versus in the distal colon. This study demonstrated that the difference in sensitivity in the proximal and distal colon was seen for adenomas 10mm or larger and CRC of Dukes’ stages C or D [25].
Flexible Sigmoidoscopy (FSIG)

This technique utilizes a flexible endoscope to view images of 40 to 60 cm of the distal colon. Cleansing of the bowel is best achieved with a single phosphate enema that can be administered at home. This procedure can be performed without any sedation. This intervention allows for small polyps up to 9 mm in diameter to be removed if needed [26]. The exam usually lasts 10-20 minutes but can take longer if a polyp is found. Common adverse effects associated with FSIG include nausea, fainting, dizziness, with the most common being bleeding [27-30]. Bleeding was seen in 8-306 per 10,000 screened [27,30]. Inflammation and bleeding requiring hospitalization was seen in 3-8 per 10,000 screened [27-29].

Three large studies, British Flex Sig Trial, Italian Score trial, and US PLCO (The Prostate, Lung, Colorectal and Ovarian) trial demonstrated that sigmoidoscopy as a screening tool lead to a 21-23% reduction in overall incidence of CRC after a followup of 11 years [26,29,31-33]. There was a reduction in the incidence of CRC in the distal colon to about 24-36% versus no reduction seen in the incidence of proximal CRC [26,33]. The Norwegian NORCCAP (Norwegian Colorectal Cancer Prevention) trial of the 4 major studies did not show a reduction in incidence of CRC but this may be due to a short follow up period of about 7 years. However, these four major trials have shown that FSIG decreases the incidence rates of CRC and also leads to a two-fold greater reduction of CRC mortality than biennial gFOBT screening. A 5 year-interval is recommended for normal FSIG exams [33].

Colonoscopy

Colonoscopy is the gold standard for screening as it allows for examination of the entire colon with the ability to remove any possible neoplasias [26,34]. Colonoscopy is an endoscopic technique utilizing a flexible, regular forward-viewing video colonoscopy that can view the entire colon. The bowel prep usually consists of a liquid diet at least one day prior, followed by a complete bowel lavage with oral laxatives. Accuracy of screening with a colonoscopy is dependent on proper bowel preparation [4,35]. It is usually performed with administration of I.V. benzodiazepine with or without an analgesic and sometimes with anesthesia.

In the National Polyp Study, a case-control done in the USA showed that adenoma removal with colonoscopy and proper surveillance during the followup period decreased the incidence of CRC rates by 76-90%. In addition, it prevented CRC mortality within the following 10 years [26,70,71]. However, these results have not been reproduced in community practice. In a Canadian population study it was seen that colonoscopy screening reduced mortality caused by distal CRC by 47-67% however it had no effect on mortality for proximal CRC [26,36,37].

Studies have shown that endoscopists miss about 2% of adenomas >1cm to about 26% of adenomas <5 mm in diameter [26,38,39]. Some studies have shown a colonoscopy miss rate of 6-12% for adenomas >10 mm [4,40]. Another study had shown that about 10% of neoplastic polyps are not completely removed [26,41]. Therefore, an effective colonoscopy is dependent on proper training, effective documentation, a clean bowel to allow for a full examination up to the cecum with adequate viewing of the mucosa, and the ability to remove polyps to send for pathological examination [4].

Advantages of the colonoscopy include being able to view the entire colon, detecting and removing any anadomas. Limitations of the test include the bowel preparation which should entail proper cleansing of the bowel. It is an invasive procedure with the risk of postpolypectomy bleeding and perforation which account for rates of about 0.1 to 0.3% [9,42,43]. The most common of the two is postpolypectomy bleeding and the chances increases with large polyps and location of the proximal colon. Other adverse effects include hypotension, arrhythmias, oxygen desaturation which account for about half of all adverse events and are usually secondary to sedation [4,44]. Current recommendations state that screening with colonoscopy every 10 years starting at the age of 50 if there are no other reasons to screen earlier is acceptable.

CT Colonography (CTC)

CT Colonography (CTC) which is also called virtual colonoscopy is an imaging modality that has been shown to be comparable to a colonoscopy in examining the entire colon and detecting clinically significant polyps and CRC [45-49]. It is considered to be less invasive than a colonoscopy [9,35,50]. In preparation for the test, patients consume a standard low-volume bowel preparation such as magnesium citrate with bisacodyl or polyethylene glycol bowel preparation alone. Tagging of colonic stool and fluid is done with 2% barium sulfate and diatrizoate respectively. Prior to CT imaging, a small rectal catheter is placed in the rectum and carbon dioxide is insufflated. CT images are acquired in 2D and 3D to determine size and location of polyps. There is no need for any I.V. sedation or analgesia [51-53].

The risk for colonic perforation compared with a colonoscopy is as low as 0.005% for asymptomatic patients [54] and up to 0.06% for symptomatic patients [55]. Another limitation is the risk posed by exposure to radiation.

The Imaging Network National CT Colonography trial consisting of 2,500 patients showed that accuracy of colonoscopy and CTC was comparable. Studies have shown a sensitivity of 89% for adenomas greater than 5mm [56,57]. The sensitivity was higher for invasive adenoma at 96% [58]. One study demonstrated that lesions >6mm at a specificity of 84.5% which increased to 97.4% for lesions >1cm [4,56,59].

An adequate CTC is dependent on good intestinal preparation, adequate insufflation of the colon, and proper training of technicians acquiring images and physicians interpreting 2D and 3D images of the colon [4,59]. Currently, all patients with one or more polyps >10mm or 3 or more polyps >6mm are advised to obtain a colonoscopy [60]. Screening should commence at the age of 50. There is not enough evidence to suggest when follow up should be obtained with a negative CTC. At this time, recommendation is to repeat the test every 5 years.

MR Colonography (MRC)

Another method is obtaining an magnetic resonance imaging of the colon. This technique similar to the CTC allows for evaluation of the entire colon. MR Colonography (MRC) does not involve the use of ionizing radiation which is one reason why it may be favored over CTC. However, it is likely a contrast agent will be unitized for both CTC and MRC [9,61]. In two meta-analysis the sensitivity of MRC was 100% in detecting CRC. When polyps were greater than 10 mm in size the sensitivity was 88% and specificity was 99% [9,61]. In a meta-
analysis comparing CTC with MRC it was found that sensitivity and specificity was 95% for both MRC and CTC [45,62,63].

**Double-Contrast Barium Enema (DCBE)**

The first radiological test to examine the entire colon was the double-contrast barium enema (DCBE). Prior to this test, a laxative should be given. During the test, the entire colon is coated with barium sulfate and air is introduced through a flexible catheter into the rectum. X-rays are taken while changing the position of the patient to assess for the presence of lesions. This procedure takes about 30 to 45 min. Studies have shown that sensitivity ranges from 50 to 80% for polyps smaller than 1 cm, 70 to 90% for polyps greater than 1 cm, and from 55 to 85% for Dukes Stage A and B [64,65]. The quality of the examination is affected by adequate bowel preparation, proper barium distribution throughout the colon, patient being able to change positions and the experience of the interpreter. Patient should undergo colonoscopy if the examination were to show a polyp of greater than 6mm. Another limitation are the side effects which include bloating and cramps. The risk of perforation is low with rates showing 1 in 25,000 for DCBE compared to 1 in 1,000 and 2,000 colonoscopies [4,66]. Patients also seem to experience more discomfort with this exam in comparison with FOBT, FSIG, and colonoscopy [4,66].

**Stool DNA**

A new technique is the use of detecting DNA, RNA and protein biomarkers in stool samples. CRC is associated with mutations in genes such as APC, K-ras, and p53. Cells from the cancer and polyps can be found in the feces. The test consists of multi-marker panel of numerous mutations since there is not one single DNA mutation present in cells. For instance, the first version of the test included mutations in APC, P53, BAT-26 and K-ras [4,67-69]. The test necessitates a stool sample that is at least 30g in weight.

Several studies have shown that sensitivity ranged from 52 to 91% and specificity ranged from 93 to 97% [4,69-75]. In a study comparing sDNA, gFOBT, and colonoscopy with 2,507 people with average risk it was found that sDNA test had a greater sensitivity of 52% in comparison to 13% for gFOBT. In addition, this study showed that sDNA had a lower sensitivity of 15.1% when detecting advanced adenomas (tubular adenoma >1cm, a villous adenoma, or an adenoma with high grade dysplasia). The sensitivity for gFOBT for advanced adenomas was much lower at 10.7% [4,59,70].

Advantage of this test is that it is not invasive and can easily be performed in the privacy of one’s home. However, this test is very expensive and if cancer is suspected the patient will need to undergo a colonoscopy. This test poses an option for those who are deterred by endoscopy as means for screening [71-73].

**FDG-PET Scan**

18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is often used to detect recurrence of CRC. FDG-PET makes use of a glucose analog FDG which is labeled with the cyclotron-produced, positron-emitting radioisotope fluorine-18. In malignancy, there is an increased uptake of glucose in comparison with the surrounding normal tissue. The focal increased FDG uptake allows one to identify the malignant tumors [74-76]. It should be noted that this uptake is nonspecific and is also seen in other inflammatory conditions with increased metabolism. Patients are asked to fast 6 hours prior to imaging. A dose of intravenous FDG is given and scanning is done after 45 minutes thereafter. Images are acquired with a tomograph in axial, coronal and sagittal planes [77].

Studies have shown that FDG-PET imaging can detect primary carcinomas and premalignant lesions of the large bowel [77-81]. The size of the lesion and grade of dysplasia plays a role in the sensitivity. The sensitivity is about 72% for a tumor larger than 1 cm and is about 33% for low grade lesions and 76% for high grade lesions [77,81]. A colonoscopy is warranted when focally increased uptake of FDG is seen in the colon. There are few studies that discuss the usefulness of FDG-PET scanning in the initial staging of CRC. The sensitivity of detection of nodal metastasis is poor and not significantly different from CT imaging. Thus, the use of this imaging modality in preoperative staging of CRC can be used but does have a significant impact on clinical management [77,82]. Other limitations of PET scan include movement of respirations and physiological uptake of 18 F-FDG into the liver and colon which can reduce the contrast resolution of the PET scan [83]. Studies have shown that FDG-PET in conjunction with CT in preoperative planning of patients with hepatic metastases has allowed for identification of additional extrahepatic disease sites in about 11-23% of cases [84].

**Discussion**

Screening can detect polyps and reduce the incidence of CRC. Current guidelines recommend screening to begin at the age of 50 years for those with average risk. Colonoscopy should be recommended for patients with a first-degree relative with either CRC or adenomatous polyps before the age of 60 or in 2 or more relatives at any age. Screening should begin at the age of 40 for such patients or 10 years prior to the youngest case of CRC in the family [59,64].

As discussed there are many different modalities available for the purpose of screening.

The choice depends on patient’s preferences for convenience, time, and money. Each test has different advantages and disadvantages.

Current recommendations state that FOBT should be done every 2 years, FIT should be done every 2 years, colonoscopy should be done every 10 years, FSIG should be done every 5 years, DCBE should be done every 5 years, and CTC should be done every 5 years. There is not enough evidence to suggest the interval follow up for sDNA.

Screening can save costs. Chemotherapy costs have gone up throughout the years and thus screening and preventing advanced CRC can prevent costs associated with cancer diagnosis. One study found that when compared with no screening, the savings from treatment by preventing CRC and deaths secondary to CRC doubled with the use of new chemotherapy agents [4,85].

Screening can reduce rates of mortality and morbidity from CRC however the rates of screening continue to be low. National CRC screening rates are about 45% which is much lower than screening rates for prostate, cervical and breast cancer [4,86]. These rates may be low due to lack of access to care, fear of screening tests, inadequate understanding of cancer risks and screening, lack of specialists, problems with referrals, etc. This seems to be a world-wide issue. In Europe, less than 25% of the population is screened [26,36]. Screening in the US tends to start at the primary care setting. In order to effectively increase screening rates, we will have to explain the importance of screening and provide patients with different options for screening.
References


autofluorescence endoscopy for adenoma detection in high-risk subjects.


