



Strategy for Colorectal Cancer Screening

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Abstract

Colorectal cancer is a leading cause of cancer death in Israel. Our current understanding of the colorectal adenoma-carcinoma sequence has led to the use of screening for timely detection of polyps and cancer. Digital examination of the rectum is a test that can be performed by all doctors. Fecal occult blood testing, flexible sigmoidoscopy and colonoscopy are the standard screening techniques for patients. Computerized tomography colonography is now entering this field. This review discusses the merits and uncertainties of these strategies as related to the risk of colorectal cancer in selected populations.

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Colorectal cancer is the commonest neoplasm in Israel after breast and prostate [1]. The annual incidence rates per 10⁵ for 1996–1997 (age-standardized to the world population) were: Jews: male 40.5, female 32.2; Arabs: male 14.2, female 11.2. Over 2,000 cases of CRC are diagnosed each year in this country and that number is increasing. The incidence is higher in Israeli-born Jews as well as in Jews immigrating from western countries. For comparison, in the United States white population the annual incidence rates of CRC per 10⁵ for 1998 (age-standardized to the world population) were higher than those of Israel – 64.4 in males and 46.8 in females [2].

The last 20 years have seen considerable advances in our understanding of the environmental, genetic and molecular basis of colorectal cancer. Changes at the chromosomal level (loss of cell cycle control checkpoints, abrogation of apoptosis, and dysregulation of intracellular signaling pathways) alter the growth characteristics of healthy colorectal epithelial cells, with formation of benign adenomas and ultimately carcinomas, the so-called adenoma-carcinoma sequence [3]. Given this knowledge, the application of screening strategies enables earlier detection of adenomatous polyps and CRC [4]. Because colorectal cancer produces few symptoms when the tumors are small and most readily curable, screening of asymptomatic patients has been advocated as a cost-effective measure to save lives. Screening refers to testing patients without specific symptoms; its major contribution lies in the detection of precancerous polyps. There is still dispute regarding

CRC = colorectal cancer

Table 1. Screening methods for colorectal cancer

- Rectal examination
- Fecal occult blood
- Sigmoidoscopy
- Colonoscopy
- CT colonography*

* Still controversial

which screening approach is optimal, the costs of the program, and how much screening can be afforded.

A good screening test must improve the lives of those screened, either by prolonging life or by improving its quality. To be effective, the test must be sensitive (i.e., it should detect all affected individuals), specific (false positives should be limited), acceptable (it should not subject individuals to excessive anxiety or extra testing), and affordable by those tested. For CRC, the primary aim of screening is to detect adenomas of the colon while they are still benign. A number of screening strategies is available [Table 1].

A broader acceptance of screening is expected to reduce the

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incidence and mortality of CRC. A “Global Campaign against Digestive Cancer” has been launched by the World Organization of Gastroenterology [5]. In this country the Israel Cancer Association (<http://www.cancer.org.il>) is conducting an intensive program to alert the population aged 50 years and older concerning CRC. While it is often stated that CRC screening is the domain of the gastroenterologist, surgeon and epidemiologist, it is in general practice that patients can most effectively be made aware of the risk of CRC. This review is aimed primarily at the family physician.

Methods of screening and their efficacy

Screening for CRC and adenomatous polyps is performed in asymptomatic men and women. Screenees are classified into two

Table 2. Classification of screened populations

| Degree of risk | Underlying pathology |
|----------------|--|
| Average | None |
| Increased | Family history of CRC |
| | Familial adenomatous polyposis |
| | Hereditary non-polyposis colorectal cancer |
| | Personal history of CRC |
| | Personal history of adenomatous polyps |
| | Inflammatory bowel diseases |

groups: The first group comprises “average risk” persons, defined by exclusion as being without any risk factors, where screening begins at age 50 years (since the risk of CRC increases exponentially with age beginning at age 50); the second group comprises “increased risk” persons, who bear one or more risk factors [Table 2] and require a screening program tailored to age and risk factors. A positive result in any screenee is followed by full clinical evaluation and treatment. Appropriate periodic surveillance is offered thereafter, again adapted to each case.

Never to be forgotten among the screening methods is the *digital rectal examination*, which every doctor must perform as part of the physical examination, and which will reveal lower rectal cancers.

Fecal occult blood testing is not expensive or invasive and is easy to perform in general practice. It has the highest patient compliance rate. The normal gastrointestinal losses of blood are about 0.5–1 ml/day [6]. Polyps in the left colon and rectum produce 54% positive tests, whereas those in the proximal colon produce positive tests only 17% of the time [7]. The standardized guaiac test is reliably negative in control subjects on restricted diets, and less than 1% of tests are falsely positive on low peroxidase diets. Hemoccult II is usually used, without hydration. Hydration increases sensitivity but reduces specificity [8]. False positive results lead to expensive and needless investigations, and steps are taken to avoid this situation. A diet must precede the test. The candidate for screening must not consume red meat and preferably also poultry and fish (all these contain non-human hemoglobin) for 3 days. Drugs and substances interfering with the test are stopped; this includes horseradish, fresh broccoli, turnips, cauliflower (which contain vegetable peroxidase) and colchicine, which give a false positive reading. Anticoagulants, aspirin or non-steroidal anti-inflammatory drugs cause leakage of blood into the intestinal tract. Oxidizing drugs (topical iodine, bromides, and boric acid) and reserpine are stopped 3 days before the test as they can cause a false positive reading. Iron colors the stool and should be stopped as well. Vitamin C causes a false negative reading. To avoid errors, the stool specimens should be examined as soon as they reach the laboratory. A trained technician makes fewer mistakes than a casual examiner. Since bleeding is erratic, many cases of CRC and adenomatous polyposis are missed by FOBT. Thus, it is recommended to test stool samples taken over 6 consecutive days. The University of Minnesota Colon Cancer Study, involving life table analysis of 235,000 person-years of exposure in test subjects and controls in an 18 year follow-up, found that CRC mortality was

FOBT = fecal occult blood testing

significantly reduced by hydrated FOBT [9]. Using rehydrated Hemoccult, as in the Minnesota study, results in substantially more positive tests but increases the cost of the program because of the need for a definitive diagnostic workup for each positive FOBT [8].

Flexible sigmoidoscopy examines the rectum and sigmoid colon, and a variable length of the descending colon up to the splenic flexure, depending on the success of the bowel preparation and the tolerance of the patient. The ratio of lesions in the proximal versus distal colon varies in different studies; it is a reasonable compromise to say that flexible sigmoidoscopy detects 50% of colorectal polyps. Flexible sigmoidoscopy is invasive and not entirely risk-free, particularly in the minority of patients where intravenous sedation is used. Polyps are removed at flexible sigmoidoscopy or at the colonoscopy which follows (except large sessile polyps crossing two folds of the colonic mucosa that require surgery). A positive flexible sigmoidoscopy makes no predictions about polyps in the remainder of the colon. Screening sigmoidoscopy does appear to contribute to a significant reduction in CRC mortality, with screened subjects having only 30% of the risk for fatal cancers of the rectum and sigmoid colon, compared with an unscreened cohort [10].

Never to be forgotten among the screening methods is the digital rectal examination

Fiberoptic colonoscopy is more invasive than flexible sigmoidoscopy, demands intensive colon preparation with Soffadex or similar cleansing agents, and requires intravenous sedation in all cases. Colonoscopy examines the entire colon in over 90% of cases, and an expert colonoscopist reaches the cecum 98% of the time. Small lesions (<5 mm) may be missed and patients must be told this at the time that the consent form is signed. Some tiny lesions do exhibit a malignant potential. In a Markov model (endpoints: cases of CRC averted, CRC deaths averted, and cost per life-year saved), colonoscopy performed every 10 years was shown to be more cost-effective than flexible sigmoidoscopy every 10 years or annual FOBT [11]. The risk of perforation or bleeding at colonoscopy is about 0.3% each [12].

Computerized tomography colonography (“virtual” colonoscopy) is being evaluated as an alternative to colonoscopy in the detection of polyps. It is a rapidly evolving method in which data from CT are used to generate two- and three-dimensional displays of the colon and rectum. CT colonography has the disadvantages of high cost and high radiation exposure, as well as patient discomfort from air insufflation of the bowel since there is no sedation. The colon is prepared as in fiberoptic colonoscopy. However, this strategy has captured the imagination of the public as being non-invasive and “safe.” The accuracy of the method is the prime question, particularly concerning small or flat polyps [13]. The data on false positive (stool misinterpreted as a polyp) and false negative (missed small lesions) detection rates have been controversial,

and much depends on the expertise of the radiologist and the sophistication of the CT equipment available. In a recent publication from the U.S. the sensitivity of CT colonography for adenomatous polyps was 94% for polyps at least 10 mm in diameter, 94% for polyps at least 8 mm in diameter, and 89% for polyps at least 6 mm in diameter [14]. In a carefully matched Dutch study, CT colonography and optical colonoscopy exhibited a similar ability to identify large polyps in patients at increased risk for colorectal cancer, but there were several missed flat lesions [15]. More comparative research is required before CT colonography will become an authentic screening method. In parallel, the accuracy of fiberoptic colonoscopy will improve as chromoendoscopy and other new methodologies become widely available. CT colonography may also reveal pathology in other abdominal organs, which is an advantage over colonoscopy.

Other screening methods, such as detection of abnormal DNA in the stool, or tumor markers in blood, remain in the experimental stage.

The remainder of this review will state the current recommendations for screening. Further reading is recommended in Rosen et al. [16] and Boland [6].

Recommendations for screening in persons of average risk

In these persons FOBT is offered yearly from age 50. It may be supplemented with flexible sigmoidoscopy every 5 years. Colonoscopy is offered every 10 years where appropriate; often this is at the patient's request. Any positive result on FOBT and/or flexible sigmoidoscopy mandates colonoscopy. The time intervals for flexible sigmoidoscopy and colonoscopy are derived from current concepts of the speed of tumor growth. It must be emphasized that 80% of CRC cases belong to this category of average-risk persons. Polyps may be present in as many as 30% of average-risk screenees at age 50 years, depending of the ethnic origin of the individual. Compared with no screening, the incremental cost-effectiveness ratio of repeat colonoscopy every 10 years was calculated to be \$10,983 per life-year saved [17].

Recommendations for screening in persons with increased risk

Persons with first-degree relatives with AP or CRC

The first-degree relatives are parent, sibling and child. The cancer develops at a young age. Indeed, the risk of CRC at age 40 is the same as that in average-risk persons aged 50. Screening therefore begins at age 40, and earlier if the family member presented with CRC at age <45 years. Colonoscopy is preferred to FOBT combined with flexible sigmoidoscopy.

Persons with first-degree relatives with familial adenomatous polyposis

These persons require genetic testing after the age of puberty to determine whether they carry the FAP gene. A negative gene test

rules out FAP only if the affected family member had an identified mutation. Flexible sigmoidoscopy is carried out in gene carriers at yearly intervals; polyps will in due course appear in the rectum if the patient expresses the phenotype. A person with FAP has a nearly 100% chance of developing CRC; such a person requires elective total colectomy!

Hereditary non-polyposis CRC

According to the Amsterdam criteria, this is a syndrome of CRC developing in three or more family members (one patient must be a first-degree relative of another patient) across at least two generations, and with one cancer diagnosed at age <50 years. Adenomatous polyps precede CRC, and both are predominantly proximal to the splenic flexure. Colonoscopy is indicated every 2 years from age 20 and yearly after age 40. Genetic testing is required, but is positive in only 80% of cases. This means the practitioner should be prepared to search for the syndrome even when all the criteria are not met. Flexible sigmoidoscopy and FOBT are inappropriate tests in hereditary non-polyposis colorectal cancer.

Some 80% of colorectal cancer cases belong to the category of average-risk persons

Persons with a personal history of CRC

Colonoscopy is required prior to surgery or within 6 months following surgery to detect synchronous polyps or cancer, next after 3 years, and if normal then every 5 years.

Persons with a personal history of adenomatous polyps

Colonoscopy is required after 3 years, and if normal then every 5 years. Closer follow-up is required in cases with flat or sessile polyps removed at colonoscopy.

Persons with inflammatory bowel disease

Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. Colonoscopic surveillance of the whole colon and serial biopsies for dysplasia is required after 7 years of disease, and is performed at 1–3 year intervals, depending on the presence and degree of dysplasia. However, there is no direct evidence that this practice cost-effectively reduces CRC mortality. The adenoma-cancer sequence is generally absent in this group, but adenomatous polyps occasionally appear. CRC in Crohn's disease is less frequent than in ulcerative colitis.

Summary

Given a busy workload, the family practitioner needs brief guidelines to identify those persons with a possible presence of colorectal polyps or CRC. While individuals with a personal history of polyps or CRC are obviously at risk, a positive family history in one or more relatives, first-degree or other, over generations or not, is a most important reason for referral to the

AP = adenomatous polyposis
FAP = familial adenomatous polyposis

gastroenterologist. Finally, patients with inflammatory bowel disease, however mild, require referral. The three terms to be remembered are therefore: personal history, family history, and inflammatory bowel disease.

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Colorectal cancer screening is particularly challenging, as reflected in current low screening rates in most countries where there is a high risk for colorectal cancer. Colorectal cancer screening is complex, as there are multiple options, it requires considerable patient effort (fecal occult blood test slides, colonoscopy preparation, etc.), and it requires sedation and a health-care partner for some tests (colonoscopy).^Â The screening strategy (test, interval, age range) should be based on medical evidence (guidelines), availability of resources, level of risk, and cultural acceptance by the population.^Â One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon.