



# Screening for colorectal carcinoma

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## ABSTRACT

Colorectal carcinoma is the second most common cause of death in Canada. Because there is a precursor lesion (that is, the polyp), screening is critically important to prevent the disease through polyp removal—and failing that, to detect colorectal carcinoma at an early stage, when it can be cured. Several screening modalities are available, but colonoscopy is considered the best. People should avail themselves of such examinations, and physicians should encourage them to do so.

## KEY WORDS

Screening, colorectal cancer

## 1. INTRODUCTION

Colorectal carcinoma is the fourth most common internal malignancy; it is second only to carcinoma of the lung as a cause of carcinoma death. It was estimated that, in 2009, 22,000 new cases of colorectal carcinoma would be diagnosed in Canada and that 9100 people would die of the disease<sup>1</sup>. The annual incidence has been increasing slightly in both men and women since 1988<sup>1</sup>. Mortality has continued to decline in both sexes, but more so among women.

Consensus is emerging internationally about the benefits of population-based screening for colorectal carcinoma. Screening is under consideration in Canada at both the provincial and the national level. In January 2007, the Ontario Ministry of Health and Long-Term Care, in collaboration with Cancer Care Ontario, launched a province-wide population-based colorectal cancer screening program: Colon Cancer Check. However, casual screening is already prevalent in Canada and may have contributed to the most recent increased incidence and decreased mortality rates. At birth, the probability of eventually developing a colorectal carcinoma in Canada is 6.5% in women and 7.4% in men. The probability of dying of the disease in Canada is 3.3% in women and 3.7% in men<sup>1</sup>.

## 2. DETECTION OF EARLY COLORECTAL CARCINOMA

Survival for colon and rectal carcinoma is closely related to the clinical and pathologic stage of the disease at diagnosis. The National Bowel Cancer Screening Programme in England clearly demonstrated downstaging of colorectal cancer with a highly significant shift toward earlier-stage disease in the screened group as compared with controls: Dukes A, 45.3% versus 10.1%; Dukes B, 21.7% versus 50.0%; Dukes C, 29.2% versus 36.3%; and Dukes D, 3.8% versus 3.5%<sup>2</sup>. It has become clear that if the disease can be detected at an early stage, overall prognosis can be improved, with the additional benefit that most colorectal carcinomas can even be prevented.

Many colorectal carcinomas are asymptomatic until a late stage, when some partial obstruction occurs, causing abdominal pain or change in bowel habits. Although carcinoma of the colon and rectum bleeds occasionally and unpredictably, it may be possible to diagnose the disease at an early stage by examining for occult blood in the stool. Through many observations and studies, including current knowledge of the molecular genetics of colorectal carcinoma, the natural history of the disease is known to start with one crypt. The numerous gene mutations slowly give rise to a small polyp, which then progresses to an invasive carcinoma that eventually metastasizes. This lengthy stepwise natural history provides a window of opportunity for detecting early carcinoma and removing polyps. Thus, to reduce morbidity and mortality and to remove premalignant polyps, a screening strategy can be directed at detecting early colorectal carcinoma, thus reducing its incidence.

### 2.1 Early Diagnosis of Colorectal Carcinoma

Colorectal carcinoma fulfils all the criteria for justified screening:

- It is common and serious: it is the second leading cause of death from carcinoma in Canada, affecting men and women equally.

- Various screening tests have been shown to achieve accurate detection of early-stage colorectal carcinomas<sup>3–7</sup>.
- Evidence from controlled trials and case–control studies suggests with varying degrees of persuasiveness that removing adenomatous polyps reduces the incidence of colorectal carcinoma and that detecting early-stage carcinomas reduces mortality from the disease.
- The benefits of screening outweigh its harms.

The various methods of screening for colorectal carcinoma all have cost-effectiveness ratios comparable to those for other generally accepted screening tests<sup>8</sup>. Of paramount importance is that colorectal cancer screening compliance in a Canadian practice setting is suboptimal, as reflected by the low proportion of screen-detected cancers compared with symptomatic presentation<sup>9</sup>. Significant effort is needed at the level of the patient, the physician, and the government to improve compliance.

## 2.2 What Is Screening?

Screening identifies individuals who are more likely to have colorectal carcinoma or adenomatous polyps from among those without signs or symptoms of disease<sup>8</sup>. The goal of screening for colorectal carcinoma is to reduce mortality from the disease.

## 2.3 Who Should Be Screened?

An estimated 40% of Canadians 50 years of age or older reported that they had colorectal cancer testing<sup>10</sup>. Approximately 75% of all new cases of colorectal carcinoma occur in people with no known predisposing factors for the disease. People with no predisposing factors are considered to be at average risk for colorectal carcinoma. People with a family history of colorectal carcinoma (that is, one or more parents, siblings, or children with the disease), but without any apparent defined genetic syndrome, account for most of those at high risk (15%–20%). Hereditary nonpolyposis colon cancer (HNPCC) accounts for 4%–7% of all cases, and familial adenomatous polyposis (FAP), for about 1%. The remainder, about 1%, are attributed to a variety of uncommon conditions: chronic ulcerative colitis, Crohn colitis, Peutz–Jeghers syndrome, and familial juvenile polyposis. Other risk factors that should be kept in mind include older age, a diet high in saturated fats and low in fibre, excessive alcohol consumption, and sedentary lifestyle<sup>11</sup>.

Screening people at average risk for colorectal carcinoma is different from screening people at high risk. Risk stratification can be accomplished by asking several questions aimed at uncovering the risk factors for colorectal cancer<sup>12</sup>:

- Has the patient had colorectal carcinoma or an adenomatous polyp?

- Does the patient have an illness (for example, inflammatory bowel disease) that predisposes to colorectal carcinoma?
- Has a family member had colorectal carcinoma or an adenomatous polyp? If so, how many? Was it a first-degree relative (parent, sibling, or child)? And at what age was the carcinoma or polyp first diagnosed?

## 3. SCREENING PEOPLE AT AVERAGE RISK FOR COLORECTAL CARCINOMA

Men and women at average risk should be offered screening.

In their most recent statement, the U.S. Preventive Services Task Force recommended screening for colorectal cancer using a fecal occult blood test (FOBT), sigmoidoscopy, or colonoscopy in adults beginning at 50 years of age and continuing until 75 years of age<sup>13</sup>. They concluded that the evidence is insufficient to assess the benefits and harms of computed tomography (CT) colonography and fecal DNA testing as screening modalities for colorectal cancer. The variety of screening options available allows patients to apply personal preference and may increase the likelihood that screening will occur. Winawer and colleagues<sup>12</sup> have stated that the best screening test is the one that gets done.

### 3.1 Fecal Occult Blood Test

Annual screening with the FOBT involves a guaiac-based test with dietary restriction or an immunochemical test without dietary restriction. Two samples from each of three consecutive stools should be examined without rehydration. Patients with a positive test on any specimen should be followed up with colonoscopy<sup>12</sup>. In the Minnesota trial, FOBT screening every other year was found to reduce colorectal cancer mortality by 21%<sup>14</sup>, a rate consistent with the results of biennial screening in the two European trials<sup>5,7</sup>. A recent Swedish study found a significant reduction in colorectal cancer mortality in a screened group as compared with a control group: 0.84 overall risk of death from colorectal cancer<sup>15</sup>. A systematic review of three clinical trials<sup>3–5,16</sup> showed that a restricted diet does not reduce the positivity rate for the older, less-sensitive guaiac-based tests and that very restricted diets may reduce compliance rates<sup>17</sup>. Disadvantages of FOBT are that currently available tests for occult blood fail to detect many polyps and some carcinomas<sup>18</sup>. Also, most people who test positive will not have colorectal neoplasia (false-positive test result) and, thus, will undergo the discomfort, cost, and risk of colonoscopy without benefit.

### 3.2 Flexible Sigmoidoscopy

Screening with flexible sigmoidoscopy is recommended every 5 years. Case–control studies have

reported that sigmoidoscopy is associated with reduced mortality for colorectal carcinoma<sup>19–21</sup>. Colon carcinoma risk in the area beyond the reach of the sigmoidoscope was not reduced. Several studies have shown that the prevalence of proximal advanced adenomas in patients without distal adenomas is in the 2%–5% range<sup>22–25</sup>. In one randomized controlled trial, screening sigmoidoscopy followed by colonoscopy when polyps are detected was associated with an 80% reduction in colorectal carcinoma incidence<sup>26</sup>.

### 3.3 Combined FOBT and Flexible Sigmoidoscopy

In combined screening, FOBT is done every year, and flexible sigmoidoscopy every 5 years. When both tests are performed, the FOBT should be done first, because a positive result is an indication for colonoscopy, obviating the need for the sigmoidoscopy examination. The combination of both screening methods is likely more effective than either method of screening alone for several reasons:

- For distal colon lesions, FOBT may be less sensitive<sup>27</sup>.
- Case–control studies report that screening FOBT and sigmoidoscopy are each associated with reduced colorectal carcinoma mortality after controlling for the other test<sup>19,28</sup>.
- A nonrandomized controlled trial reported a 43% reduction in colorectal carcinoma deaths in people screened with FOBT and sigmoidoscopy relative to sigmoidoscopy alone<sup>4</sup>.

### 3.4 Colonoscopy

In two cohort studies of people with adenomatous polyps, colonoscopy has been shown to reduce the incidence of colorectal carcinoma<sup>29,30</sup>. Colonoscopy permits detection and removal of polyps and biopsy of carcinoma throughout the colon. However, colonoscopy involves greater cost, risk, and inconvenience to the patient than other screening tests, and not all examinations visualize the entire colon. Choice of a 10-year interval between screening examinations for average-risk people (if the preceding examination is negative) is based on estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop. The dwell time from the development of adenomatous polyps to transformation into carcinoma is estimated to be at least 10 years on average<sup>29,31</sup>. Others believe that the transformation time from polyp to carcinoma takes 5–8 years<sup>32</sup>, and so many endoscopists, including this author, recommend colonoscopy every 5 years.

In two large prospective studies of screening colonoscopy, about half the patients with advanced proximal neoplasms had no distal colonic neoplasms<sup>23,24</sup>. Similarly, in a prospective study of distal colon findings, 65% of a cohort of average-risk people with carcinoma proximal to the splenic

flexure were found to have no neoplasm distal to the splenic flexure<sup>33</sup>. In a study to determine the propriety of using the presence of distal adenomas as an indicator for colonoscopy, our group found that, in 153 patients with no distal adenomas, 54% had non-advanced proximal adenomas, and 33% had advanced adenomas<sup>34</sup>. Thus, the absence of distal adenomas should not negate the indication for colonoscopy. A randomized controlled trial compared sigmoidoscopy with follow-up colonoscopy for all patients having polyps with no screening and demonstrated a significant reduction in colorectal carcinoma incidence in the screened patients<sup>26</sup>.

### 3.5 Double-Contrast Barium Enema

Double-contrast barium enema (DCBE) is recommended every 5 years. No randomized trials have evaluated whether screening DCBE reduces the incidence or mortality from colorectal carcinoma in people at average risk of the disease. The sensitivity of DCBE for large polyps and carcinomas is substantially less than that of colonoscopy<sup>35</sup>, the procedure does not permit removal of polyps or biopsy of the carcinomas, and DCBE is more likely than colonoscopy to identify artefacts and other findings (such as stool) as polyps. Patients with an abnormal barium enema need a subsequent colonoscopy. Here, DCBE is included as an option because it offers an alternative (albeit less sensitive) means to examine the entire colon, and the procedure is widely available.

## 4. SCREENING PEOPLE AT INCREASED RISK FOR COLORECTAL CARCINOMA

### 4.1 Family History of Colorectal Carcinoma or Adenomatous Polyp

Significant evidence indicates that carcinomas arise at an earlier age in people with one or more first-degree relatives (parent, sibling, or child) who have been diagnosed with colorectal carcinoma or adenomatous polyps at less than 60 years of age than in average-risk people. In effect, the risk in a 40-year-old person with a family history of colorectal carcinoma is comparable to that in an average-risk 50-year-old person<sup>36</sup>. Screening colonoscopy should be started at 40 years of age, or at 10 years earlier than the earliest diagnosis age in the family, whichever comes first, and should be repeated every 5 years<sup>12</sup>.

### 4.2 Genetic Syndromes

Patients with genetic syndromes should undergo genetic counselling and genetic testing, a subject beyond the scope of this treatise<sup>37,38</sup>. Pre-symptomatic genetic testing removes the necessity of annual screening in at-risk individuals who lack the relevant gene and probably improves compliance in those who do

have it. Individuals whose pre-symptomatic DNA diagnosis indicates that they have the FAP-causing gene should have annual colon and rectal examinations with at least a flexible sigmoidoscopy beginning at approximately 10 or 11 years of age<sup>39</sup>. The age for the start of screening varies from series to series. The St. Mark's series began at 14 years of age or older<sup>40</sup>. Follow-up surveillance for extra colonic neoplasms is also indicated. Patients should also be counselled about the risk of FAP for future offspring.

Screening recommendations for HNPCC have varied, but the recommendation for gene carriers has been colonoscopy beginning at age 20–25 years or at least 5 years earlier than the earliest age at which colon carcinoma was diagnosed in a particular kindred. The procedure should be repeated every other year until the patient is 30 years of age and then annually thereafter<sup>41</sup>. The frequency of colonoscopic examination is justified by the finding that HNPCC adenomas have repair-deficient cells with rapidly and relentlessly accumulating mutations that support the clinical concept of “aggressive adenomas” and accelerate the adenoma–carcinoma sequence.

## 5. NEW SCREENING TESTS

Two emerging screening tests have promising potential.

### 5.1 CT Colonography

Computed tomography colonography (CTC)—“virtual colonoscopy”—is a novel technique for colorectal examination. The CTC examination is performed with a helical CT scanner. A bowel preparation similar to that for colonoscopy is required. This relatively new technique was first described by Vinning *et al.*<sup>42</sup> in 1994.

As a screening study for colorectal carcinoma, CTC has these potential advantages<sup>43</sup>:

- The possibility that the study may one day be performed without prior bowel preparation.
- The possibility of greater patient acceptability (not yet proven).
- The potential for screening for important disease outside the colon.

The accuracy of CTC varies widely among reported series. Two recently published reports of rigorously conducted multicenter randomized trials showed similar sensitivities of 84% and 80% for clinically significant adenomas (>9–10 mm) in average- and high-risk cohorts respectively<sup>44,45</sup>. For diminutive ( $\geq 5$  mm) adenomas, performance was poorer at 65%–72%<sup>44,45</sup>. For colorectal cancers, the CTC miss rate was not trivial at approximately 6%<sup>44,45</sup>. More recently, Johnson<sup>46</sup> noted that, with the publication of the National CT Colonography Trial and the endorsement of CTC for screening by a multi-society task force that included the American Cancer Society, the American College

of Radiology, and the U.S. Multi-Society Task Force on Colorectal Cancer, CTC is now ready for widespread clinical application. On the other hand, the Centers for Medicine and Medicaid Services in the United States denied reimbursement for CTC, stating that the evidence was inadequate to justify the use of this screening modality<sup>47</sup>. At present, CTC seems reasonable in patients with incomplete colonoscopy or who are poor candidates for colonoscopy, although DCBE is also a good choice and costs less. It also makes sense to do CTC (with intravenous contrast) in patients with obstructive colon carcinoma<sup>48</sup>.

### 5.2 Fecal DNA Testing

Fecal DNA testing is based on the idea that, because carcinoma is a disease of mutations that occur as tissue evolves from normal to adenoma to carcinoma, those mutations should be detectable in stool. Preliminary reports that people with advanced carcinoma show detectable DNA mutations in stool<sup>49</sup> provided the basis for a large study, using a panel of 21 mutations, in more than 4000 asymptomatic people who received screening colonoscopy, fecal DNA testing, and FOBT with Hemoccult II (Beckman Coulter, Brea, CA, U.S.A.)<sup>50</sup>. Sensitivity and specificity for fecal DNA testing for colorectal cancer screening have recently been reported as 87.5% and 82% respectively<sup>51</sup>. Such stool-based testing is appealing because it is noninvasive, requires no special colonic preparation, and has the capability of detecting neoplasia throughout the entire colon.

## 6. SUMMARY

Colorectal cancer is a disease that is, for the most part, preventable, treatable, and beatable. Because almost all colorectal cancers have a precursor lesion, the polyp, a concerted effort must be made to eradicate those lesions, thus saving the lives of countless people—not to mention dollars in a health care system already severely stressed for resources.

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