



# Prevention of Colorectal Cancer

Although advances are being made in managing colorectal cancer when it is diagnosed, prevention should be the major focus. Prevention through screening is an established method for halting the progression from benign to malignant disease.

**By Martin S. Friedlich MD, MSc, MEd, FRCSC; and  
Hartley S. Stern MD, FRCSC, FACS**

**I**n Canada in 2001, 17,174 people were diagnosed with colorectal cancer and 6,438 people died from the disease.<sup>1</sup> The average risk of developing colorectal cancer over one's lifetime is 5% to 6%. When the disease is localized, the five-year survival rate is approximately 90% for colon cancer and 80% for rectal cancer, however, 65% of

patients present with advanced disease. It is, therefore, imperative that every effort be made to identify patients with colorectal cancer at an early stage. A further enhanced strategy would be to try and prevent the development of colorectal cancer in the first place.

Dr. Friedlich is assistant professor, department of surgery, University of Ottawa, and colorectal surgeon, Ottawa Hospital, Ontario.

Dr. Stern is professor and chairman, department of surgery, University of Ottawa, colorectal surgeon, The Ottawa Hospital, and CEO, Ottawa Regional Cancer Centre, Ontario.

Prevention of colorectal cancer can be divided into two categories —primary prevention and secondary prevention — based on the fact that colorectal cancer develops from benign polyps (adenomas). Primary prevention refers to preventing the development of polyps so they do not have the opportunity to develop into cancer. Secondary prevention refers to halting the process of progression from a polyp to a cancer.

## Primary Prevention

Primary prevention of colorectal cancer can be thought of in three categories:

- Avoidance of noxious substances, including dietary or environmental;
- Chemoprevention, including ingestion of naturally occurring substances that may be part of one's diet, or synthetic compounds, such as medications; and
- Prophylactic colectomy in certain patients determined to be at high risk.

**Dietary and environmental.** Environmental and dietary factors are believed to be important etiological factors in 85% to 90% of all cases of colorectal cancer.<sup>2</sup> High-fibre diets have been studied extensively as a way of inhibiting the development of colorectal cancer. Proposed mechanisms as to how dietary fibre may exert its protective effect include changes in gut flora and increased stool bulk, with dilution of potential substances, or a more brief exposure of mucosa to potential carcinogens.<sup>3,4</sup> In randomized studies, there has been no conclusive evidence that diets high in fibre reduce the incidence of colorectal cancer.<sup>5</sup>

Dietary fat enhances cholesterol and bile acid synthesis, and anaerobic bacteria in the colon convert these compounds to secondary bile acids, which has been shown to induce malignant degeneration in animals.<sup>6</sup> Despite this finding in animals, in human studies to date, low-fat diets have

not been shown to reduce the risk of colon cancer.<sup>7</sup>

Calcium's ability to act as a colon cancer prevention agent is conflicting. Although some studies have shown calcium is capable of suppressing increased epithelial proliferation, other studies have contradicted this and have demonstrated no reduction in proliferative indices.<sup>7-9</sup>

Some studies suggest people who are physically active could be at a reduced risk of developing colon cancer. Possible mechanisms for this effect include those that are protective against all cancers and those that may be specific to colorectal cancer. For example, it is possible increased physical activity is a marker for other health behaviours that may be protective against cancer. There may be an exercise-induced slowing of the immunologic response to aging.<sup>10</sup> Moderate exercise has been shown to decrease bowel transit time significantly, therefore, reducing contact time between fecal carcinogens and colonic mucosa, and decreasing the risk of colon cancer.<sup>11</sup>

**Chemoprevention.** Nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated as a chemopreventive agent for colorectal cancer. They appear to reduce the incidence of disease, reduce growth rate and induce differentiation or apoptosis in gut epithelial cells.<sup>12</sup> Several studies, involving patients with familial adenomatous polyposis (FAP), have been carried out to test the efficacy of sulindac. These studies showed partial, and in some cases, complete, regression of colorectal adenomatous polyps. All patients, however, experienced regrowth of these polyps after sulindac was stopped.<sup>13</sup>

Despite these initial promising results, further enthusiasm regarding the ability of NSAIDs to decrease the risk of colon cancer was lacking, due to the potential negative effects of long-term NSAID use, including gastrointestinal (GI) irritability. The mechanism of these drugs is through the inhibition of the enzyme cyclooxygenase

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(Cox). Their toxicity is also mediated through this enzyme. Research has shown Cox exists in at least two isoenzymes, Cox-1 and Cox-2. Presumably, selective inhibitors of Cox-2 could serve as chemopreventive agents. Since it is the Cox-1 enzyme that mediates the negative effects of these drugs, it was hypothesized that if one could develop products that could inhibit Cox-2 without Cox-1, this would allow the products to attain a maximal therapeutic effect with little or no toxicity. Overexpression of Cox-2 has been observed in colon tumors. Celecoxib was developed for this purpose. Unlike NSAIDs, which inhibit both forms of the Cox enzyme, celecoxib inhibits Cox-2 preferentially. Studies have shown dietary administration of celecoxib inhibited both the incidence and the multiplicity of colon tumors by 93% and 97% respectively in populations of FAP patients. The drug is currently the subject of investigation in sporadic polyps.<sup>14</sup>

**Prophylaxis.** Molecular biological advances have made it possible to develop tests to identify people at a much higher risk of colorectal cancer. Germline mutations can be identified, including adenomatous polyposis coli (APC) in FAP and mutator genes in hereditary colorectal cancer (HNPCC).<sup>15</sup> After identification of germline mutations for HNPCC, prophylactic colectomy is indicated because the lifetime risk for colorectal cancer is 80%.<sup>16</sup>

Patients who have had longstanding inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer.<sup>17</sup> The risk of colorectal cancer in patients with ulcerative colitis has been determined to be 30%, 35 years after diagnosis of pancolitis.<sup>18</sup> Patients with ulcerative colitis and sclerosing cholangitis are at even higher risk of dysplasia or cancer of the colon. These cancers occur more commonly on the right side and are believed to be due to the higher concentration of carcinogenic secondary bile acids found in

the proximal colon.<sup>19</sup> In patients with Crohn's disease, segments of bowel that are excluded, such as a rectal stump, are at increased risk of malignant change. By recognizing this increased risk, physicians can help prevent the development of cancer by removing the bowel at risk. This can be considered a form of primary prevention.

## Secondary Prevention

Secondary prevention refers to halting development of a colorectal cancer from an adenomatous polyp. This occurs by excision of the polyp, usually by a colonoscope. The method by which one detects these polyps is called screening. In order to have a successful screening program, one must determine who to screen and how best to screen. High-risk patients make up 25% of the population and include those with first-degree relatives who have had colorectal cancer, patients with inherited syndromes and some patients with IBD. Evidence shows cancer arises at an earlier age in patients with a first-degree family member who has had the disease. In addition, the incidence of colorectal cancer in this group is twofold that of the general population. Furthermore, the risk is higher if the relative developed colorectal cancer at a younger age.

Common screening modalities include fecal occult blood testing (FOBT), flexible sigmoidoscopy, double contrast barium enema (DCBE) and colonoscopy. Trials using FOBT for screening show a decreased death rate from colorectal cancer, presumably by identifying earlier stages of cancer. Such screening is reported to have a sensitivity of 92%. Adding flexible sigmoidoscopy every five years to annual FOBT increases carcinoma prevention 2.2-fold. The most common preparation for FOBT uses guaiac peroxidase — a hydrogen peroxide reagent that turns colourless guaiac blue in the presence of hemoglobin (Hgb) (using the peroxidase activity of Hgb).

Table 1

## U.S. Recommendations: Screening Average-Risk Patients

	Recommendation	Age to commence
Asymptomatic: no risk factors	DRE and one of the following: FOBT and flex sigmoidoscopy	50
CRC in non first degree relative	or Total colon examination (colonoscopy or DCBE and sigmoidoscopy)	

DRE = digital rectal examination; FOBT = fecal occult blood testing; CRC = colorectal cancer;  
DCBE = double contrast barium enema

False-positive results can occur, due to substances that can cause GI bleeding, such as acetylsalicylic acid (ASA) and NSAIDS. Furthermore, dietary sources of Hgb, including red meat and peroxidase in some fruits and vegetables, can cause false-positives. False-negative results can occur if the cancer is not bleeding at the time of the test, if the patient has consumed antioxidants or if the colour change is masked by iron supplementation. Meta-analysis has showed a reduction in mortality rate of 23%.<sup>20</sup>

DCBE has been shown to have a sensitivity of 50% to 80% for polyps < 1 cm, 70% to 90% for polyps > 1 cm and 55% to 85% for early stage colorectal cancer. It is estimated that DCBE detects between 85% and 95% of colorectal cancer.<sup>21</sup>

Flexible sigmoidoscopy has been proposed as a modality for screening, since up to two-thirds of neoplasms are within the theoretical reach of the 60-cm instrument. Flexible sigmoidoscopy has been estimated to detect 50% to 60% of colorectal cancer.<sup>22</sup> Colonoscopy detects more cases of polyps < 9 mm, as compared to DCBE and flex sigmoidoscopy combined. There is no difference, however, between groups in the number of patients with detected carcinomas or polyps > 9 mm.

Advantages of colonoscopy over other screening tests include the fact that FOBT detects only those polyps and cancers that bleed. Flex sigmoidoscopy allows inspection of only the distal half of the large bowel and DCBE does not allow biopsy or polypectomy. Colonoscopy has been shown to have an overall sensitivity of 90% for polyps > 1 cm.<sup>23</sup>

The U.S. has come up with recommendations on screening for colorectal cancer (Tables 1 to 3).<sup>24</sup> Canada has adopted recommendations for high-risk patients, but has not developed a screening program for the average-risk patient.

People with a family history of FAP also should be considered for genetic counselling and consider genetic testing to determine if they are gene carriers.<sup>21,25</sup> A negative genetic test result rules out FAP only if an affected family member has an identified mutation.<sup>26</sup> Gene carriers or indeterminate cases should be offered flexible sigmoidoscopy. If genetic tests are negative, screening should be the same as for low-risk individuals.

Proposals for colorectal cancer screening programs have been made in British Columbia and Ontario, and are at different stages of implementa-

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Table 2

## U.S. Recommendations For Screening Moderate-Risk Patients

	Recommendation	Age to commence
CRC in first-degree relative age $\leq$ 55, or two or more relatives of any age	Colonoscopy	40 or 10 years before youngest case in family
CRC in first-degree relative > age 55	Colonoscopy	50 or 10 years before age of case

Table 3

## U.S. Recommendations for High-Risk Patients

	Recommendation	Age
Family history of FAP	Flex sigmoidoscopy Consider counselling Consider genetic testing	12 to 14 (puberty)
Family history of HNPCC	Colonoscopy Consider counselling Consider genetic testing	21 to 40
IBD Left-sided colitis Pancolitis	Colonoscopy Colonoscopy	15th year after diagnosis Eighth year after diagnosis

FAP = familial adenomatous polyposis; HNPCC = hereditary colorectal cancer; IBD = inflammatory bowel disease

tion. These recommendations suggest the program should be available to all individuals aged > 50, and that FOBT be used as the primary modality. Individuals with an abnormal FOBT result also should be offered accurate examination of the entire colon (colonoscopy or DCBE plus flex sigmoidoscopy). The proposed recommendations also suggest the program be expanded to include the option of direct visualization of the entire colon as a primary screening modality. This

should occur only when the program is assured there is sufficient colonoscopy and DCBE to provide timely assessment of FOBT individuals, high-risk and symptomatic individuals.

## Conclusion

Colorectal cancer is the third-leading cause of cancer deaths in Canada and, therefore, represents an important health concern. Although advances

are being made in managing the disease when it is diagnosed, prevention should be the major focus. Dietary and environmental forms of primary prevention have been tested, but, so far, none have been shown to reduce the risk of colorectal cancer in randomized controlled trials. Trials of new chemopreventive agents are ongoing and promising. Secondary prevention through screening is an established method for halting the progression from benign to malignant disease. Although there is a general acceptance of screening guidelines for moderate and high-risk individuals, a screening program for average risk individuals has not yet been established. [CME](#)

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