Colon cancer – Screening family members: Who, when and at what intervals?

COLORECTAL CANCER (CRC) IS THE SECOND LEADING CAUSE OF death from cancer in Canada, with an annual incidence of 45 per 100,000.[1] In the United States, mortality from CRC has declined steadily since 1950 even though the incidence has increased.[2] This experience has been echoed in the United Kingdom.[3] One cannot ignore the possibility that early detection and therapy have played a role. This is especially true because the successful treatment of CRC depends on the cancer's size at detection. The understanding of the adenomatous polyp to cancer sequence makes screening intuitively appealing, and indirect evidence is emerging that suggests a survival benefit from general population screening programs with flexible sigmoidoscopy.[4]

The average lifetime risk of CRC is about 5%.[5] This translates into a lifetime risk of dying from CRC at 2.5%. Population studies have demonstrated a two- to threefold increased risk of colon cancer in first-degree relatives of index cases. A similar risk of colon cancer is present in first-degree relatives of individuals with adenomatous polyps. When two or more primary relatives are affected, the colon cancer risk increases ninefold over baseline.[5] Affected second-degree relatives (grandparents, aunts, uncles) impart somewhat less risk than affected first-degree relatives. There are also 'cancer family syndromes' wherein endometrial, ovarian, gastric, bile duct, small bowel and transitional carcinomas are associated with an increased risk of CRC.

Age at diagnosis also appears to be an important factor in determining familial risk. If the index case is diagnosed at age 55 or older, the risk in first-degree relatives is double that of the general population. The risk triples with an index case of age 45 to 54, and is four times the risk in the general population if the index case is diagnosed at age younger than 45. A recent prospective, controlled study of colonoscopy in asymptomatic first-degree relatives of CRC patients showed that male sex, increasing age and as few as one first-degree relative with CRC are statistically significant risk factors for the development of colonoscopically detectable colon adenomas.[6]

For these reasons, The Canadian Task Force on the Periodic Health Examination recommends "that periodic sigmoidoscopy or colonoscopy be performed among people at increased risk of colorectal cancer (ie, first-degree relatives of patients with colorectal cancer and women with a history of endometrial, ovarian or breast cancer)".[1]

Ransohoff and colleagues[7] believe it is appropriate to screen persons who have two or more first-degree relatives with CRC, with the use of annual fecal occult blood tests and periodic endoscopy (sigmoidoscopy or colonoscopy) after age 40.

While there is agreement that persons with an increased risk should have periodic screening, optimal strategies have not been agreed on. Until the underlying genetic mechanisms are clarified one must rely on recommendations gleaned from the literature, and these will be highlighted.

Even without a full understanding of the cause of CRC it is still helpful to classify the disease based on the family history of cancer and additional phenotypic information to help target surveillance and management strategies.

'Hereditary' CRC is defined as a family history of CRC occurring in an autosomal dominant pattern that may also involve certain phenotypic signs depending on the specific disorder (ie, florid adenomatous polyps, benign and malignant extracolonic lesions, cancer of unusually early onset and multiple primary cancers, particularly synchronous and metachronous CRC).[4] The 'familial' type occurs when at least one first-degree relative has CRC. The 'sporadic' type occurs in the absence of a family history of CRC. Hereditary CRC includes familial adenomatous polyposis (FAP), hereditary flat adenoma syndrome (HFAS) and hereditary nonpolyposis colon cancer (HNPCC or 'Lynch syndromes').

FAP accounts for only a small percentage of the overall cancer risk (0.2%) yet it is the best known hereditary CRC syndrome. FAP includes various disorders with the common feature of multiple polyps in the colon. Traditionally the phenotype was characterized by diffuse carpeting of the entire colonic mucosa with adenomatous polyps. In reality the spectrum ranges from discrete polyps to complete coverage of the mucosa. FAP patients may have polyps with various other histologies in addition to adenomas. The presence of extracolonic signs, such as those seen in Gardner's syndrome, and cancers at diverse anatomical sites (gastric, adrenal, thyroid) also characterize this disorder. More importantly, the gene for FAP has been located on the long arm of chromosome 5 (5q15-22) and is called the *apc* (adenomatous polyposis coli) gene. Screening programs incorporating genetic linkage data and using various probes on chromosome 5q are being developed for the preclinical diagnosis of FAP.4 Genetic testing for affected family members is available.

For FAP patients the recommendations are:

–if genetic markers can determine the mutant gene, those affected should have flexible sigmoidoscopy every three years from age 10 to 40;

–screening should continue (although less often) in those without the gene until genetic markers are sufficiently accurate to approach 100% sensitivity and specificity;[8]

–if the polyposis phenotype is identified, prophylactic colectomy is indicated and surveillance should begin with a side-viewing endoscope for gastric, duodenal and periampullary polyps. This should continue every one to three years.

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HFAS has also been linked to chromosome 5q. The onset is later in life and the polyps are flat, predominantly right-sided and usually number less than 100.

Baseline colonoscopy is recommended at age 25 for HFAS and should be repeated at five-year intervals if normal until age 35, with the procedure repeated annually thereafter. Scattered polyps may be managed endoscopically but if they number more than 20 per year – and if any CRC exists – a subtotal colectomy should be offered.

The HNPCC syndromes include site-specific colon cancer (Lynch I) and the cancer family syndrome (Lynch II). These represent about 5% of the total CRC risk and are autosomal dominant with 100% penetrance. In contrast to FAP and HFAS, where the abnormality seems to be an 'adenoma' gene, HNPCC seems to be a cancer gene whereby any adenoma that happens to develop becomes cancerous. The gene is not located on chromosome 5 and studies linking it to chromosome 18 are disputed.[4] A detailed clinical history is critical if appropriate therapy (subtotal colectomy because of the high risk of subsequent colon cancer) and screening is to be offered to family members. For practical purposes, affected families can be defined if there are three or more first-degree kin with CRC.[9]

Screening recommendations for HNPCC include colonoscopy every two years from age 25 (or five years earlier than the earliest colon cancer in the family). For Lynch II members, endometrial vacuum curettage beginning at age 25, mammograms, Papanicolaou smears and transvaginal ultrasound examinations of the ovaries and uterus are advised.

Inherited genetic factors are also important in familial CRC and may play a large role in sporadic CRC. One must also bear in mind that many sporadic cases may be familial but the history is lacking. Conversely, by chance alone two familial cases may not share a genetic predisposition since the disease is so common. Pedigree analysis indicates that a partially penetrant autosomal dominant inherited susceptibility to adenomas and CRC is common, and that this allows dietary and other factors to determine which susceptible patients will develop adenomas and cancer.[7] The United States' National Cancer Institute believes there is evidence to support reducing the risk of colon and other cancers by modifying eating patterns, particularly of fat and fibre. Their recommendations are:[2]
–reduce fat intake to 30% or less of calories;
–increase fibre intake to 20 to 30 g/day;
–include various vegetables and fruits in the daily diet;
–avoid obesity;
–drink alcohol only in moderation;
–minimize consumption of salt-cured, salt-pickled or smoked food.

Guidelines for familial CRC are:
–if there is one affected first-degree relative, standard screening should begin at age 35 to 40 (including annual digital rectal examination and fecal occult blood testing, with flexible sigmoidoscopy every three to five years). Many advocate colonoscopy every five years beginning at age 40;[6]
–for two affected first-degree relatives, annual fecal occult blood testing and colonoscopy every three to five years starting at age 35 to 40 (or five years younger than the earliest age of onset in the affected kin) is recommended;
–if there are three or more affected first-degree relatives or if colon cancer had been diagnosed in a first-degree relative before age 30, HNPCC should be suspected and screening carried out as described.

Guidelines for postpolypectomy screening may require modification in view of recent evidence showing that single, small (less than 1 cm), tubular adenomas do not increase the risk of cancer.[10,11]

Recommendations for postpolypectomy surveillance as summarized by Bond are:[12]
–complete colonoscopy at the time of polypectomy to detect and resect all synchronous adenomas;
–repeat colonoscopy in three years;
–selected patients with multiple adenomas or suboptimal clearing may require colonoscopy at one and four years;
–after one negative three-year follow-up examination, surveillance interval may be increased to five years;
–surveillance should be individualized and discontinued when it appears unlikely that continued follow-up is capable of prolonging life expectancy;
–patients with one small tubular adenoma (less than 1 cm) do not have an increased risk of cancer, and therefore follow-up surveillance may not be indicated.

Recommendations for surveillance after curative resection of a colorectal cancer are:
–colonoscopy should be performed preoperatively to clear any synchronous lesions. If this is not possible because of obstruction, clearing colonoscopy should be done three to six months postoperatively if no metastases are present;
–repeat colonoscopy should be performed every three years;
–serial rectal evaluation (digital, proctoscopy) is indicated in patients undergoing sphincter-sparing low anterior resection of rectal cancers.

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