

CHAPTER 6 SCREENING BASED ON FAMILY HISTORY OF COLORECTAL CANCER

Interest in hereditary predisposition to Colorectal Cancer has increased greatly over the past 15 years, largely because of identification of the genes associated with familial adenomatous polyposis (FAP) and hereditary non-polyposis Colorectal Cancer (HNPCC). Both disorders have an autosomal-dominant mode of transmission within families and carry a very high risk for cancer. In untreated FAP, mutation carriers have a lifetime risk for Colorectal Cancer close to 100%. In HNPCC, their risk for colorectal or other syndrome cancers is 70–90%. (See Chapter 7 for further information.)

This chapter discusses cancer risk and recommendations for screening for the large number of people in the community who have a family history of Colorectal Cancer, but whose family history does not have the clinical features suggestive of either FAP or HNPCC.

6.1 Cancer risk in relatives of patients with common Colorectal Cancer or adenoma

Early cancer mortality studies indicated that first-degree relatives of patients with common Colorectal Cancer (i.e. Colorectal Cancer that is not associated with FAP, HNPCC, chronic ulcerative colitis, or other recognised causes) themselves have a three- to four-fold increase in lifetime risk for Colorectal Cancer.^{1,2} However, studies of cancer incidence, in which there were appropriately matched control groups and stringent methods for collection of family cancer data in relatives, reported only a doubling of this lifetime risk.^{3–6} Relative risk was increased 1.6-fold for women and 1.9-fold for men in the Danish study, 1.8-fold for those with just one affected relative in the Australian study, and 1.7-fold and 2.2-fold in the United States studies.

In contrast to those modest levels of increased risk, Colorectal Cancer risk was shown to be substantially (three- to six-fold) greater for those who have a first-degree relative with Colorectal Cancer diagnosed at an early age (below 45 or 55 years) or when two close relatives have had Colorectal Cancer, irrespective of the age at diagnosis.^{4–6}

The observed increases in risk may be due in part to shared dietary and lifestyle factors (see Chapter 2), either alone or in combination with predisposing genetic factors. Genetic epidemiological studies indicate that inherited genetic predisposition accounts for familial clustering of Colorectal Cancer in at least some of these families, even though the mode of transmission and risks associated with the putative low-penetrance genes remain uncertain.^{7,8}

Several studies have shown that colorectal adenomas are also a marker for risk of Colorectal Cancer in other family members.^{9–11} Risk appears to be greater when adenomas are detected at an early age^{9,10} and when adenomas have advanced histological features (see Chapter 9).¹¹ Although this is a cause for concern, information from prospective studies is needed before confident recommendations can be made about special screening protocols for relatives of adenoma patients.

6.2 Practical issues related to assessment and screening

All too frequently, clinicians fail to inquire about family history of cancer. In a Swedish population-based audit of patients with Colorectal Cancer, a family medical history was documented in only 1% of the cases at the time of first presentation with symptoms.¹²

Medical information that patients provide about their relatives is often inaccurate.^{4,13–16} Given its potential importance, every effort should be made to collect reliable information. When there is uncertainty, more detailed information should be obtained from other family members, from death certificates, or from medical records. If a family medical history appears to be significant but

diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a familial cancer clinic.

When discussing cancer risk and screening, it may help to combine estimates of relative risk with absolute risk for the general population, as shown in Chapter 3. Calculations based on present age and applying to the next 5–10 years puts risk into better perspective than calculations limited to life-time risk.

6.3 Quantifying risk based on family history

Individuals can be placed in one of three categories of relative risk based on their family history.

Category 1 — those at or slightly above average risk

Asymptomatic people fit into this category if they have:

- no personal history of bowel cancer, advanced adenoma, or chronic ulcerative colitis, and
- either no close relatives with bowel cancer or one first-degree or second-degree relative with bowel cancer diagnosed at age 55 years or older.^{4-6,17}

For those with an affected first-degree relative, risk is *double* the average risk, although most of that extra risk is expressed after the age of 60 years. When the affected relative is second-degree (e.g. a grandparent, uncle or aunt), lifetime risk is increased only 1.5-fold.⁶

Category 2 — those at moderately increased risk

Asymptomatic people fit into this category if they have:

- one first-degree relative with bowel cancer diagnosed before the age of 55 years (without the potentially high-risk features listed below),^{4,6,18-20} or
- two first-degree *or* one first- and one second-degree relative(s) on the same side of the family with bowel cancer diagnosed at any age (without the potentially high-risk features listed below).¹⁹⁻²¹

Relative risk in these two situations is increased *three- to six-fold*.

Category 3 — those at potentially high risk

Asymptomatic people fit into this category if they have:

- three or more first-degree or a combination of first-degree and second-degree relatives on the same side of the family diagnosed with bowel cancer (suspected HNPCC),²² or
- two or more first-degree or second-degree relatives on the same side of the family diagnosed with bowel cancer, including any of the following high-risk features:
 - multiple bowel cancers in the one person
 - bowel cancer before the age of 50 years
 - at least one relative with cancer of the endometrium, ovary, stomach, small bowel, renal pelvis, ureter, biliary tract or brain (suspected HNPCC, see Chapter 7),²² or

- at least one first-degree relative with a large number of adenomas throughout the large bowel (suspected FAP),²³ or
- somebody in the family in whom the presence of a high-risk mutation in the APC (adenomatous polyposis coli) gene or one of the mismatch repair (MMR) genes has been identified.^{23,24}

Without genetic testing and in the absence of phenotypic features of FAP, the lifetime risk for cancer in these groups is at, or close to, 1 in 2 (relative risk increased about 15-fold). For those shown to carry a high-risk genetic mutation or to have polyposis or other features of FAP, the risk rises even further without medical intervention.

The approach to managing people in category 3 is considered in detail in Chapter 7.

Table 6.1 Familial clustering of the common forms of bowel cancer

Family history	Relative risk
One first-degree relative with bowel cancer diagnosed at 55 years or over (included in category 1)	up to 2-fold
One first-degree relative with bowel cancer diagnosed under 55 years	3 to 6-fold
Two first-degree relatives with bowel cancer diagnosed at any age	3 to 6-fold

Note: Relative risk is the ratio of the risk of developing Colorectal Cancer in a particular exposed group to the average risk in the whole population (*cf* absolute risk; see Table 3.1).

6.4 Screening recommendations

It should be noted that the following recommendations are based on studies of cancer risk and on yield of lesions in screening studies, not on randomised controlled trials with Colorectal Cancer mortality as the outcome.

Category 1 — those at or slightly above average risk

Most people with a family history of Colorectal Cancer are in this category. Their levels of risk are similar to those associated with cigarette smoking, high alcohol intake or obesity.²⁵⁻²⁷ In subjects who have just one affected relative, diagnosed when 55 years or older, the yield of clinically significant lesions at screening colonoscopy is low.^{21,28-31}

A number of organisations, including the American Cancer Society and the American Gastroenterological Association, do not consider that the slight increase in degree of risk for this group justifies more invasive screening than that recommended for the general population.^{32,33} The Australian Health Technology Advisory Committee (AHTAC) Report on Colorectal Cancer Screening concluded that recommendations for people in this category should be the same as for the average-risk population.³⁴

What recommendations are there for bowel cancer screening for those at category 1 risk?

Guidelines — Screening (category 1 risk)	Level of evidence	Practice recommendation	Refs
Faecal occult blood testing (FOBT) every second year from the age of 50 years.	See Chapter 3 and AHTAC recommendations (Box 3.1)	Recommend	3–6, 21, 28–31
Consider sigmoidoscopy (preferably flexible) every five years from the age of 50 years — average risk	See Chapter 3 and AHTAC recommendations III-3	Recommend	3–6, 21, 28–31

Category 2 — those at moderately increased risk

In category 2, the risk for Colorectal Cancer is increased approximately three- to six-fold.^{4,6,18–21} People in this situation are classified as having a moderately increased risk of Colorectal Cancer. Despite that, 70–90% of people in the group will never develop Colorectal Cancer.

It is recommended that the at-risk relatives be referred for colonoscopy at five-yearly intervals starting at age 50, or ten years younger than the age of the earliest diagnosis of Colorectal Cancer in the family, whichever comes first.³⁴ The recommendation that some should start colonoscopy before age 50 years needs to be kept under review. In one Australian audit, few significant lesions were found in category 2 subjects under 50 years of age despite the diagnosis of cancer at an early age in many index cases in that study.³⁵ Similarly, a recent Scottish study on category 2 subjects has also questioned the value of colonoscopic screening before the age of 50 years.³⁶

Family members should be advised that colonoscopy is not without risk as it is an invasive procedure (see Chapter 8 for details). Flexible sigmoidoscopy and double contrast barium enema³⁴ or CT colonography may be offered if colonoscopy is contra-indicated for some reason.³⁷

A number of steps are important in managing people within this group.

1. Because of the possibility of HNPCC, a complete family history should be taken and updated regularly, and the accuracy of the cancer diagnoses and polyp pathology should be checked carefully.
2. People at category 2 risk should be advised that genetic testing is not appropriate at present. Tumour testing for HNPCC-related changes, using immunohistochemistry and microsatellite instability, should be considered when any of the revised Bethesda criteria are met (see Chapter 7).
3. As with all forms of screening, those at risk should be carefully checked for the presence of symptoms that might be due to colorectal neoplasia. Where symptoms are present, appropriate diagnostic steps should be taken before entry into a screening program.

What recommendations are there for bowel cancer screening for those at category 2 risk?

Guidelines — Screening (category 2 risk)	Level of evidence	Practice recommendation	Refs
Offer colonoscopy every five years starting at age 50, or at an age ten years younger than the age of first diagnosis of bowel cancer in the family, whichever comes first. Flexible sigmoidoscopy and double contrast barium enema ³⁴ or CT colonography may be offered if colonoscopy is contraindicated for some reason.	III-2	Recommend	4–6, 35,36

Category 3 — those at potentially high risk

Fewer than 5% of Colorectal Cancers occur under category 3 conditions.

Members of families with either FAP or definite or suspected HNPCC are at potentially high risk for bowel cancer and, depending on the syndrome, for cancer at certain other sites.^{23,24,38,39} Members of these families should be considered for genetic testing. Those shown to carry their family-specific mutation or having uncertain genetic status require careful cancer screening (see Chapter 7 for details).

The risk for some people with three (or more) relatives with bowel cancer may be difficult to categorise, especially if all cases of bowel cancer occur at an advanced age, are confined to one generation of the family, and if no-one in the family has had any of the extra-colonic cancers associated with HNPCC.⁴⁰ Family size should be taken into account when assessing these families. If there is uncertainty about their status, it may be safer to categorise multi-case families as having suspected (or possible) HNPCC. New diagnoses of cancer in the family or results of microsatellite instability (MSI), immunohistochemical staining (IHC) or genetic testing may clarify the situation.

Recommendations for category 3 are to be found in Chapter 7.

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