Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp

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INTRODUCTION

A family history of colorectal cancer (CRC) can increase the risk that an individual will develop CRC over a lifetime. Familial CRC is a result of interactions among genetic and lifestyle factors; the amount of increased risk varies widely depending on specifics of the family history [1]. For a small proportion of people, genetic predisposition is the dominant risk factor. For most people, lifestyle factors (eg, diet, exercise, smoking, and obesity) are stronger risk factors [2,3].

This topic review describes assessment of the degree of CRC risk using information obtained from the family history, and CRC screening approaches based on the level of risk due to family history.

Strategies for screening of average-risk patients, tests available for screening, other CRC risk factors, CRC prevention strategies, and molecular genetics of CRC are described in detail separately.

- (See "Screening for colorectal cancer: Strategies in patients at average risk".)
- (See "Tests for screening for colorectal cancer".)
- (See "Colorectal cancer: Epidemiology, risk factors, and protective factors".)
- (See "Molecular genetics of colorectal cancer".)

ASSESSING RISK DUE TO FAMILY HISTORY

A family history of colorectal cancer (CRC) is common. Among the general population, 5 to 10 percent of United States adults aged 20 to 79 years report having a first-degree relative (FDR), defined as a close blood relative (ie, parent, full sibling, or child) with CRC [4]. Other countries have somewhat higher rates, with a study from the Netherlands finding that 11.7 percent of adults aged 30 to 70 years reported at least one FDR with CRC [5].

Each component of the family history (eg, recognized familial genetic syndromes, the number of FDRs with CRC and their ages at diagnosis, and the family history of documented advanced adenomas or serrated lesions) helps to determine whether the patient's risk of CRC is increased and the magnitude of the impact of the family history on the individual's risk of developing CRC.

Familial colorectal cancer history (non-syndromic) — The family history should include the number of FDRs with CRC and their ages at diagnosis. Just knowing that there is some family history, without determining age of onset, degree of relatedness, and number of affected family members, is not a strong predictor of who will develop CRC.

For most people, if a family member had CRC, it was a "nonsyndromic familial" (also called "familial") CRC, rather than a high-risk genetically heritable familial cancer syndrome. Risk for familial CRC is highest if there are multiple FDRs with CRC or an FDR who developed CRC at age <50 years [6-10]. The increase in lifetime risk with familial CRC ranges from about two- to sixfold. Estimates of these risks are shown in a figure (figure 1) [7]. Among patients who have CRC, 25 percent have a family history that placed them at increased risk [11].

A study of screening colonoscopy among people aged 45 to 75 years found that 11 percent of people with an FDR with CRC had advanced neoplasia, compared with 6 percent of those without an FDR with CRC (odds ratio [OR] 2.41; [95% CI 1.69-3.43]) [12]. Other studies have found similar results and also found that risk is somewhat higher if the index case was female or had distal CRC [13]. In another study, risk for CRC is greater for relatives of patients with colon, rather than rectal, cancer [8].

Although CRC occurring only in distant relatives has been associated with an increased risk of CRC in family members, the magnitude of the increase in risk (relative risk [RR] 1.82, 95% CI 1.47-2.25) is not large enough to warrant more screening than is recommended for the general population [7,8].

Although direct evidence from prospective studies is not available, we believe that for people who have one or more FDRs with CRC at any age, colonoscopy-based CRC screening should

start at age 40 years and be done every five years [9,14,15]. For individuals not willing to undergo colonoscopy, FIT or MT-DNA stool test may be a reasonable substitute [16].

Family polyp history — Having an FDR with an adenomatous colon polyp increases the patient's risk for adenoma and for CRC [17-22]. Several studies suggest that a family history of an advanced adenoma increases risk of CRC, regardless of the age at diagnosis of the relative. In a population-based study of 126,936 patients who underwent colonoscopy, an elevated risk of CRC was found in FDRs (RR 1.35, 95% CI 1.25-1.46), second-degree relatives (SDRs; RR 1.15, 95% CI 1.07-1.23) of adenoma cases, and FDRs of advanced adenoma cases (RR 1.68, 95% CI 1.29-2.18) compared with controls [20,23]. There is no evidence that a family history of non-advanced adenoma significantly increases risk to the patient [24,25].

A systematic review found that having an FDR with an adenoma was associated with CRC (RR 1.99 [95% CI 1.55-2.55]) compared with having no family history of adenoma [4]. However, the magnitude of risk due to a family polyp history may have been overestimated because of increased efforts to look for cancer in families who already have a history of colorectal neoplasia.

The US Multi-Society Task Force (MSTF) on Colorectal Cancer recommends that, if there is documentation that an FDR had an advanced adenoma (adenoma ≥1 cm, or with high-grade dysplasia, or with villous elements) or polyp requiring surgical excision, this should be weighted the same as having an FDR with CRC when suggesting screening programs [26]. The yield of screening colonoscopy in patients with FDRs who had advanced adenomas is substantially increased. However, the MSTF no longer recommends that patients undergo intensified colon screening without clear documentation that an FDR's polyp was advanced; in the absence of documentation that an FDR's polyp was advanced, it should be assumed it was not advanced. In our experience, patients often do not know what type of polyp their relative had, which is consistent with the finding that individuals often do not know what type of polyp they had in the past [27].

MSTF recommends that if an FDR had a documented advanced serrated lesion (SSP ≥10 mm, SSP with cytologic dysplasia, or traditional serrated adenoma ≥10 mm), screening should be similar to that of a patient whose FDR had documented advanced adenoma, although there is no clear evidence as to how to proceed unless the FDR meets criteria for serrated polyposis [26]. (See "Overview of colon polyps", section on 'Sessile serrated polyps and traditional serrated adenomas' and "Overview of colon polyps", section on 'Serrated polyposis syndrome'.)

High-risk familial colorectal cancer syndromes — A small proportion of people with a family history of CRC have one of the high-risk genetically heritable familial cancer syndromes that

substantially increase the risk of CRC. Some of these syndromes increase the risk of other cancers too. A pattern suggesting the possibility of a high-risk genetically heritable familial cancer syndrome (eg, Lynch syndrome [hereditary nonpolyposis colorectal cancer (HNPCC)] or familial adenomatous polyposis [FAP]) may become apparent when obtaining a family history. Patients may recognize the name of an inherited syndrome, if asked.

- Lynch syndrome-related cancers occur at an early age (commonly in the 30s and 40s, with median onset at age 61 years in mutation-positive relatives) (figure 2) [28,29]. Lynch syndrome is characterized by a strong family history (eg, multiple family members, across generations, developing CRC and other cancers at an early age). However, CRC patients without obvious family histories can still have the syndrome and carry a Lynch syndrome gene [30].

  With Lynch syndrome, polyps have an increased tendency to develop into CRC and an increased rate of progression to CRC. Although polyps do not occur more frequently, they can occur at an early age [31]. Lynch syndrome is caused by autosomal dominant, highly penetrant genetic mutations.

  Genetic testing for Lynch syndrome is warranted if an FDR has been diagnosed with Lynch syndrome. However, a patient may have an FDR with Lynch syndrome and not know it. Although genetic testing for Lynch syndrome has been recommended by some groups for patients diagnosed with CRC, this testing is not universally performed [32]; additionally, the patient may be unaware of an FDR's diagnosis. Additional indications for testing for Lynch syndrome are described separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Indications for germline testing'.)

  Lynch syndrome and related cancers are described in detail separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

- Familial adenomatous polyposis (FAP)-related cancers develop beginning in the 20s, and nearly 100 percent of people with FAP develop CRC, usually before age 50 years (figure 2). Hundreds to thousands of polyps occur throughout the colon, beginning as early as adolescence (picture 1). FAP is caused by autosomal dominant, highly penetrant genetic mutations.

  FAP is described in detail separately. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis".)

Another hereditary syndrome that increases CRC risk is *MUTYH*-associated polyposis (MAP). Individuals with MAP have multiple colorectal adenomas and estimated lifetime CRC risk of 70 to 75 percent. Approximately 60 percent of patients with MAP have CRC at presentation. MAP is an autosomal recessive polyposis syndrome. Among patients with CRC, <1 percent are homozygous for MAP. Heterozygotes (1 to 2 percent of the general population) have only marginally increased CRC risk of 5 to 7 percent. (See "*MUTYH*-associated polyposis".)

Additional high-risk hereditary syndromes that increase CRC risk (eg, juvenile polyposis syndrome [JPS], Cowden syndrome, Li-Fraumeni syndrome, attenuated FAP [AFAP], Peutz-Jeghers syndrome, serrated (hyperplastic) polyposis syndrome, and others detected by cancer gene panels) are discussed in detail separately. (See "Juvenile polyposis syndrome" and "PTEN hamartoma tumor syndromes, including Cowden syndrome" and "Li-Fraumeni syndrome" and "Familial adenomatous polyposis: Screening and management of patients and families", section on 'AFAP' and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "Overview of colon polyps", section on 'Serrated polyposis syndrome' and "Next-generation DNA sequencing (NGS): Principles and clinical applications", section on 'Cancer screening and management'.)

When to assess family history — Assessment of family history of CRC or colon polyps among FDRs should begin at the initial visit. Although there are no studies addressing frequency of reassessment, some clinicians reassess every three to five years as long as the patient is eligible for continued screening based on their age and any comorbidities.

Assessing family history before age 40 years identifies patients who warrant screening earlier than the usual starting age for average-risk patients, and those who also warrant genetic testing.

Family history evolves over time; thus, assessment of family history should be repeated periodically as the patient matures. Family members may develop cancers that affect the suggested frequency of screening for the patient. For example, a study using a United States population-based cancer registry found that at age 30 years, 2.1 percent of participants met criteria for more aggressive screening based upon a family history of CRC, whereas at age 50 years, 7.1 percent met the criteria for high-risk screening [33]. (See 'Screening approach' below.)

Obtaining a family history of CRC to guide screening may be cost-effective, with a cost per year of life gained similar to that of other widely accepted technologies [34]. However, family history is often not elicited or incorporated into patient care. In a survey of patients aged 35 to 55 years, 39 percent reported that they had not been asked about family history, 46 percent with a

strong family history did not know they should be screened at an earlier age, and 55 percent with a strong family history had not received appropriate screening [35].

Limitations of narrative histories and prediction tools — The patient's age, family size (which, if small, can mask recognition of a genetic mutation as the cause of cancer in a family), as well as the possibility of uncertain paternity, should be taken into account when interpreting a narrative history or results from a prediction tool.

Studies show that a patient's report of family history may be inaccurate. In a population-based study in Connecticut, people were asked about CRC family history among FDRs and SDRs, and a sample of the responses was confirmed using registries, Medicare databases, medical records, and death records. The sensitivity of patient report about their relatives was 27.3 percent, with a positive predictive value (PPV) of 53.5 percent overall (86 percent for FDRs and 44 percent for SDRs) [36]. In another study, comparing patient self-reports of their own polyp history with medical record data, the positive predictive value for self-reported polyp was 80.9 percent and the negative predictive value was 85.8 percent [37].

Prediction tools are not commonly used to assess the impact of family history on CRC risk. Generally, limitations of such tools include assumptions made about the impacts of individual risk and protective factors and interactions among them.

SCREENING APPROACH

For patients who have a family history of colorectal cancer (CRC) or documented advanced adenoma or serrated lesion but do not have a high-risk genetically heritable familial cancer syndrome, the information obtained during family history is used to guide age to initiate screening, frequency of testing, and type of screening test to choose.

There are no randomized controlled trials of screening in people with a family history of colorectal cancer. Screening recommendations for people with a family history of CRC are based upon extrapolation from evidence of effectiveness in average-risk people, modified by knowledge of how a family history affects the biology of colon polyp formation and progression to CRC. (See "Screening for colorectal cancer: Strategies in patients at average risk".)

Indications for enhanced screening — Specific aspects of the family history of CRC influence the age at which to begin screening and the frequency of screening.

Obtaining family history permits determination of the number of FDRs diagnosed with **ANY** of the following:

- Colorectal cancer (CRC)
- Documented advanced polyp with ANY of the following:
  - Advanced adenoma
    - Adenoma size ≥1 cm
    - Adenoma with high-grade dysplasia
    - Adenoma with villous elements
  - Advanced serrated lesion
    - Sessile serrated polyp (SSP) ≥1 cm
    - Traditional serrated adenoma ≥1 cm
    - SSP with cytologic dysplasia

We suggest using the information about first-degree relatives (FDRs) with **ANY** of the above to screen as follows, in keeping with the 2021 NCCN guidelines [38]:

- **One or more FDR diagnosed at any age** – Begin screening at age 40 years, or 10 years before the FDR's diagnosis, whichever is earlier (or in the case of an advanced polyp, at the age of diagnosis of the advanced polyp if that is earlier). We suggest colonoscopy every five years. If the patient declines colonoscopy, annual fecal immunochemical testing (FIT) should be offered.

If the **only** family history is an FDR with a polyp **NOT clearly documented** as an advanced adenoma or serrated lesion, we suggest that the patient be screened as an average-risk patient, because of the potential inaccuracy of the family history. This is in contrast to patients whose FDR has a **documented** history of an advanced adenoma or serrated lesion, who should be screened similarly to those with a family history of CRC, as indicated above. (See 'Family polyp history' above.)

Age to begin screening — We initiate screening at age 40 years or 10 years before youngest FDR's diagnosis (or in the case of an advanced polyp, at the age of diagnosis of the advanced polyp if that is earlier), as part of enhanced screening recommendations. (See 'Indications for enhanced screening' above.)

For patients with a family history, the rationale for beginning screening at age 40 years or 10 years before the age of diagnosis of the youngest FDR is that CRCs in such patients may occur early in life, not uncommonly in the 40s or even the 30s (figure 3) [39]. The patient's risk at age 40 years is therefore generally comparable to an average-risk person's risk at age 50 years,

which is the usual age at which average-risk people begin screening. Relative risk is greatest in the 30s and 40s and decreases as a person ages (figure 4) [40]. Beginning to screen 10 years before the age the cancer was diagnosed in the affected relative takes into account the additional risk related to early-onset CRC in the family member.

How often to screen — We screen with colonoscopy every five years. We note that in the case of advanced polyps, the 2021 NCCN guidelines recommend repeating screening every five to ten years. Due to lack of evidence supporting a specific screening interval and based on expert opinion, we utilize the more conservative end of this range (every five years) [15].

There is evidence that colonoscopy for screening should be repeated at five-year intervals in people with a family history of CRC. In the Nurses' Health Study and the Health Professionals Follow-up Study, colonoscopy screening reduced CRC risk for only five years for those with an FDR with CRC [41]. For individuals with an FDR with CRC, CRC risk was reduced within five years of colonoscopy (hazard ratio [HR] 0.44 [95% CI, 0.30-0.66]); however, CRC risk returned essentially to baseline beyond five years (HR 0.91 [95% CI, 0.55-1.52]), whereas for average-risk individuals with a negative family history, there was no difference in CRC risk less than or more than five years after colonoscopy (HR 0.42 [95% CI, 0.35-0.51] and 0.43 [95% CI, 0.32-0.58], respectively). (See "Tests for screening for colorectal cancer", section on 'Colonoscopy'.)

If the patient declines colonoscopy, and FIT is used for screening, it is performed annually. (See "Tests for screening for colorectal cancer", section on 'Fecal immunochemical test (FIT) for blood'.)

Choosing a screening test — Colonoscopy is the preferred test for patients at higher risk, as defined above (see 'Indications for enhanced screening' above). Among screening tests, colonoscopy has the highest sensitivity for CRC and for adenomas (figure 5). If the patient refuses colonoscopy, FIT testing, considered by the US Multi-Society Task Force (MSTF) to be a “tier 1” test for CRC screening, is the suggested alternative and is performed annually [26,42,43]. Specifics of tests for screening for CRC are discussed separately. (See "Tests for screening for colorectal cancer", section on 'Fecal immunochemical test (FIT) for blood' and "Tests for screening for colorectal cancer", section on 'Colonoscopy' and "Screening for colorectal cancer: Strategies in patients at average risk", section on 'Choosing a screening test'.)

Colonoscopy has better sensitivity than FIT stool testing for advanced adenomas and, in some studies, for CRC as well [16,44]. In a meta-analysis, one-time FIT sensitivity for CRC was 79 percent and, for advanced adenoma, 30 percent [26,42,43]. In one study, in which the threshold for a "positive" FIT in a quantitative assay was set intentionally low (≥10 micrograms hemoglobin/gram of feces), annual FIT for three years detected all CRC but only 61 percent of

advanced adenomas in FDRs of patients with CRC [16]. However, in another study, 572 asymptomatic individuals with a positive family history for CRC, but without a suspected or known familial polyposis syndrome or Lynch syndrome, underwent screening by both one colonoscopy and one FIT [44]. Endoscopists were blinded as to FIT results. FIT was found to have low sensitivity (adenoma 9.5% [95% CI, 5.7-15.3], advanced neoplasm 35.1% [95% CI, 20.7-52.6], and CRC 25.0% [95% CI, 1.3-78.1]). Among patients who were FIT-negative, colonoscopy detected 24 advanced neoplasms (4.7 percent of individuals who were FIT-negative) and three CRCs (0.6 percent of individuals who were FIT-negative).

Patients who refuse to undergo colonoscopy should be encouraged to undergo CRC screening with another screening test. For such patients, FIT or MT-sDNA stool test may be attractive alternatives because they are noninvasive [26,42,43]. However, maintaining the screening schedule can be a challenge because FIT should be repeated annually. A positive FIT or MT-sDNA stool test requires timely follow-up with colonoscopy. (See "Tests for screening for colorectal cancer", section on 'Advantages and disadvantages'.)

When to stop screening — Although there is no direct evidence to guide when to end CRC screening among people with a family history, the MIcrosimulation SCreening Analysis (MISCAN)-Colorectal Cancer Model suggested that CRC screening should end at age 79 among persons with one FDR diagnosed after age 50, and end at age 85 for persons with two or more FDRs diagnosed before age 40 [5], unless the patient has a life expectancy less than 10 years. Continuing to screen until age 80 or 85 years is reasonable because the absolute risk of CRC attributable to family history increases with age, since the risk is cumulative [8,40]. For example, the risk of a 70-year-old developing CRC in the next 10 years is about 9 percent if that person has at least two FDRs with CRC, compared with 3 percent in the general population [8].

HIGH-RISK SYNDROME SCREENING

Enhanced colon cancer screening and consideration of genetic testing are warranted for patients with a personal or family history of certain high-risk genetic syndromes.

Cancer screening strategies, genetic testing, and colorectal cancer (CRC) prevention for each of the following syndromes are discussed in detail separately:

- **Lynch syndrome (hereditary nonpolyposis colon cancer [HNPCC])** (see "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management")

- **Familial adenomatous polyposis (FAP)** (picture 1) (see "Familial adenomatous polyposis: Screening and management of patients and families")
- ***MUTYH*-associated polyposis (MAP)** (see "*MUTYH*-associated polyposis")
- **Juvenile polyposis syndrome (JPS)** (see "Juvenile polyposis syndrome")
- **Cowden syndrome** (see "PTEN hamartoma tumor syndromes, including Cowden syndrome")
- **Li-Fraumeni syndrome** (see "Li-Fraumeni syndrome")
- **Attenuated FAP (AFAP)** (see "Familial adenomatous polyposis: Screening and management of patients and families")
- **Peutz-Jeghers syndrome** (see "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management")
- **Serrated (hyperplastic) polyposis syndrome** (see "*MUTYH*-associated polyposis")

RISK FACTOR MODIFICATION

It is prudent to make a special effort to modify behavioral risk factors in people already at increased risk due to family history of colorectal cancer (CRC). Increased physical activity, reduced red meat intake and an increase in plant-based foods in the diet, the potential use of certain medications (eg, aspirin, nonsteroidal antiinflammatory drugs [NSAIDs]), and smoking cessation are associated with a reduction in risk for colorectal cancer. However, the risks of bleeding due to aspirin must be taken into account [45]. Risk factor modification and the use of NSAIDs or aspirin is described in detail separately. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Protective factors' and "NSAIDs (including aspirin): Role in prevention of colorectal cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for colorectal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Colon and rectal cancer screening (The Basics)")
- Beyond the Basics topic (see "Patient education: Screening for colorectal cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Assessing for risk due to family history** – One in four patients with colorectal cancer (CRC) has a family history of CRC. Only a few percent of patients with CRC have a high-risk genetically heritable familial cancer syndrome. (See 'Assessing risk due to family history' above.)
    - Familial CRC results from the interaction of genetic and environmental causes. Several polymorphisms have been identified that are statistically associated with CRC, but with the exception of high-risk genetic syndromes such as Lynch syndrome (hereditary nonpolyposis colon cancer [HNPCC]), familial adenomatous polyposis (FAP), and *MUTYH*-associated polyposis (MAP), these associations appear to account for little of the observed familial risk. (See 'Assessing risk due to family history' above.)
- **Indications for enhanced screening** – All patients should be asked before age 40 years about family history to identify those at increased risk. Assessment of family history may be repeated every three to five years and interpreted keeping in mind family size (which, if

small, can cause false-negative reports) and the possibility of uncertain paternity. (See 'Indications for enhanced screening' above.)

- **High-risk familial colorectal cancer syndromes** – The most common high-risk genetically heritable familial cancer syndromes with elevated rates of CRC are Lynch syndrome (HNPCC) and familial adenomatous polyposis (FAP). Enhanced CRC screening, tailored specifically to the disease pattern of each cancer syndrome, and consideration of genetic testing are warranted for patients with a personal or family history of certain high-risk genetic syndromes. (See 'High-risk syndrome screening' above and 'High-risk familial colorectal cancer syndromes' above.)

- **Approach to screening** – There are no randomized, controlled trials of screening in people with a family history of CRC. Screening recommendations for these patients are extrapolated from studies and recommendations for average-risk patients as well as from observational studies of people with familial CRC, modified by the known biology of familial CRC. (See 'Screening approach' above.)

  - Individuals at highest risk due to high-risk familial CRC syndromes should be screened for CRC with colonoscopy at frequent specified intervals based on current guidelines. (See 'High-risk syndrome screening' above.)

  - For other patients with a family history of CRC, advanced adenoma, or advanced serrated lesion with high-risk features described above, we suggest enhanced rather than average-risk screening (**Grade 2B**) (see 'Indications for enhanced screening' above). Specific recommendations for enhanced screening if there is one or more FDR diagnosed at any age are as follows: Begin screening at age 40 years, or 10 years before the FDR's diagnosis, whichever is earlier. We suggest colonoscopy every five years. If the patient declines colonoscopy, annual fecal immunochemical testing (FIT) should be offered. (See 'Indications for enhanced screening' above.)

  - Screening for patients at average risk for CRC is described separately. (See "Screening for colorectal cancer: Strategies in patients at average risk".)

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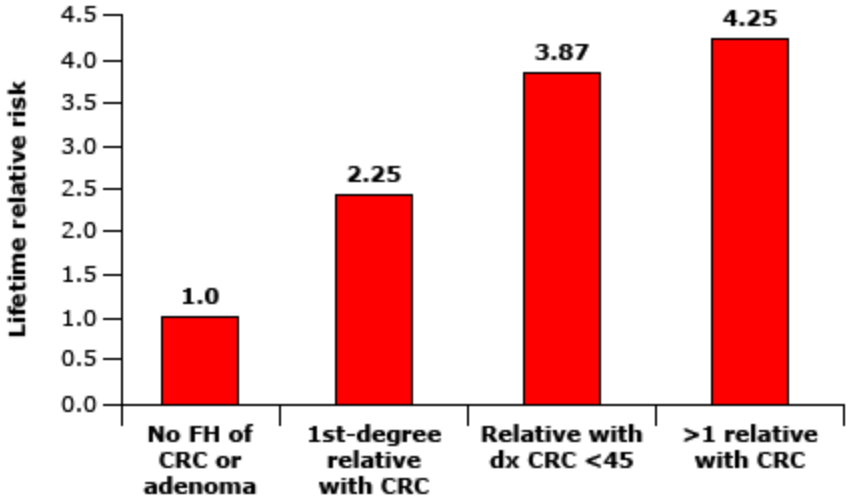
Topic 7572 Version 65.0

GRAPHICS

Risk of colon cancer associated with a family history



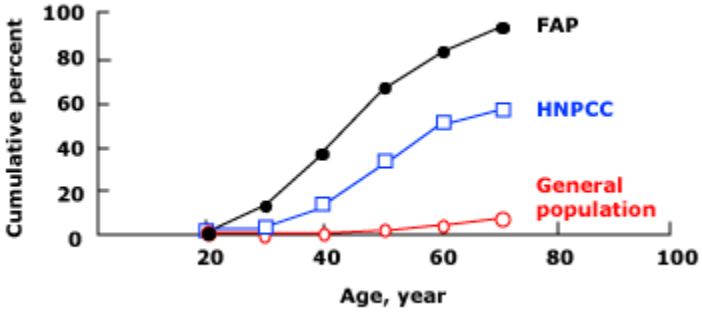
The highest risk is in people with multiple first-degree relatives or relatives who have developed CRC at a relatively young age.

FH: family history; CRC: colorectal cancer; dx: diagnosis.

Data from: Johns LE, Houlston RS. Am J Gastroenterol 2001; 96:2992.

Graphic 59834 Version 5.0

Cumulative incidence of colorectal cancer by age in subjects with genetic syndromes compared with the general public

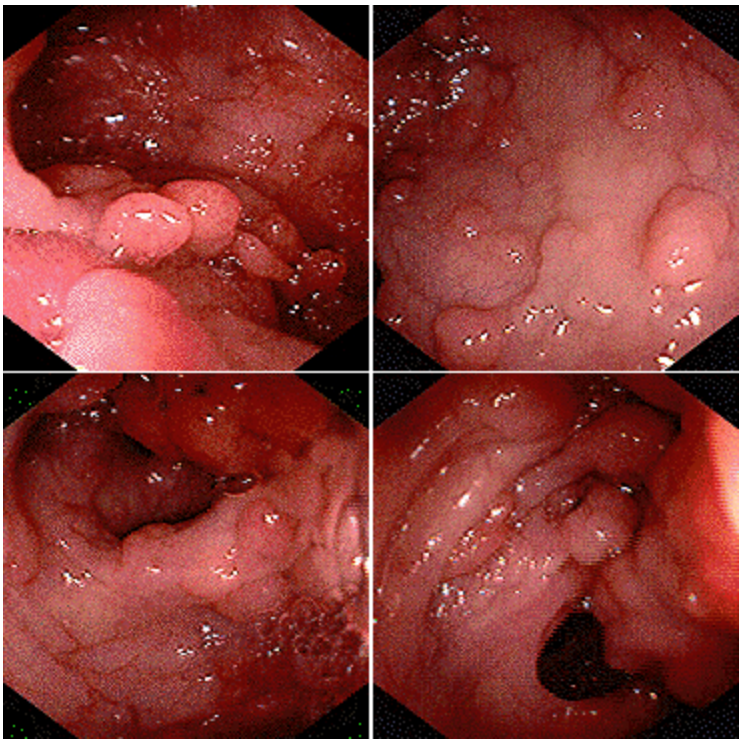


FAP: familial adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer.

Data from: Winawer SW, Fletcher RH, Mille L, et al. AGA guidelines: Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology 1997; 112:594.

Graphic 58291 Version 2.0

Endoscopic appearance of multiple polyps in familial adenomatous polyposis

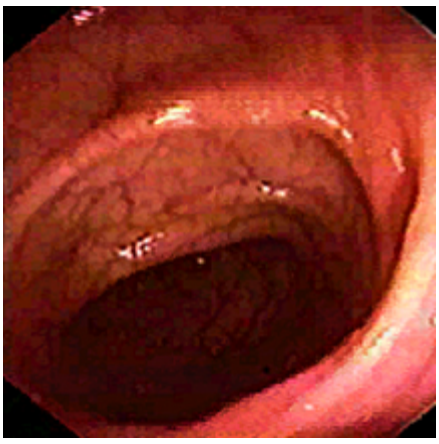


Endoscopic findings at multiple levels in a 50-year-old man with familial adenomatous polyposis. Multiple polyps of various sizes are seen. At colectomy, some of these polyps had areas of high-grade dysplasia and early malignant transformation.

Courtesy of James B McGee, MD.

Graphic 59413 Version 2.0

Normal sigmoid colon

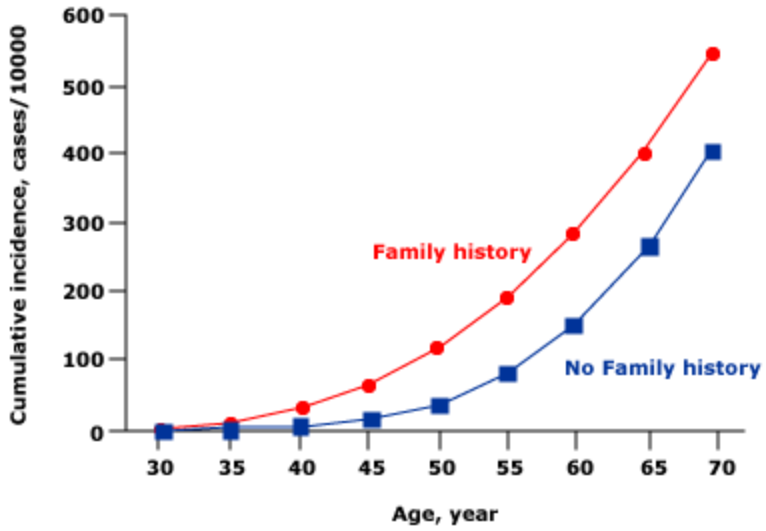


Endoscopic appearance of the normal sigmoid colonic mucosa. The fine vasculature is easily visible, and the surface is shiny and smooth. The folds are of normal thickness.

Courtesy of James B McGee, MD.

Graphic 55563 Version 1.0

Incidence of colorectal cancer according to age and family history

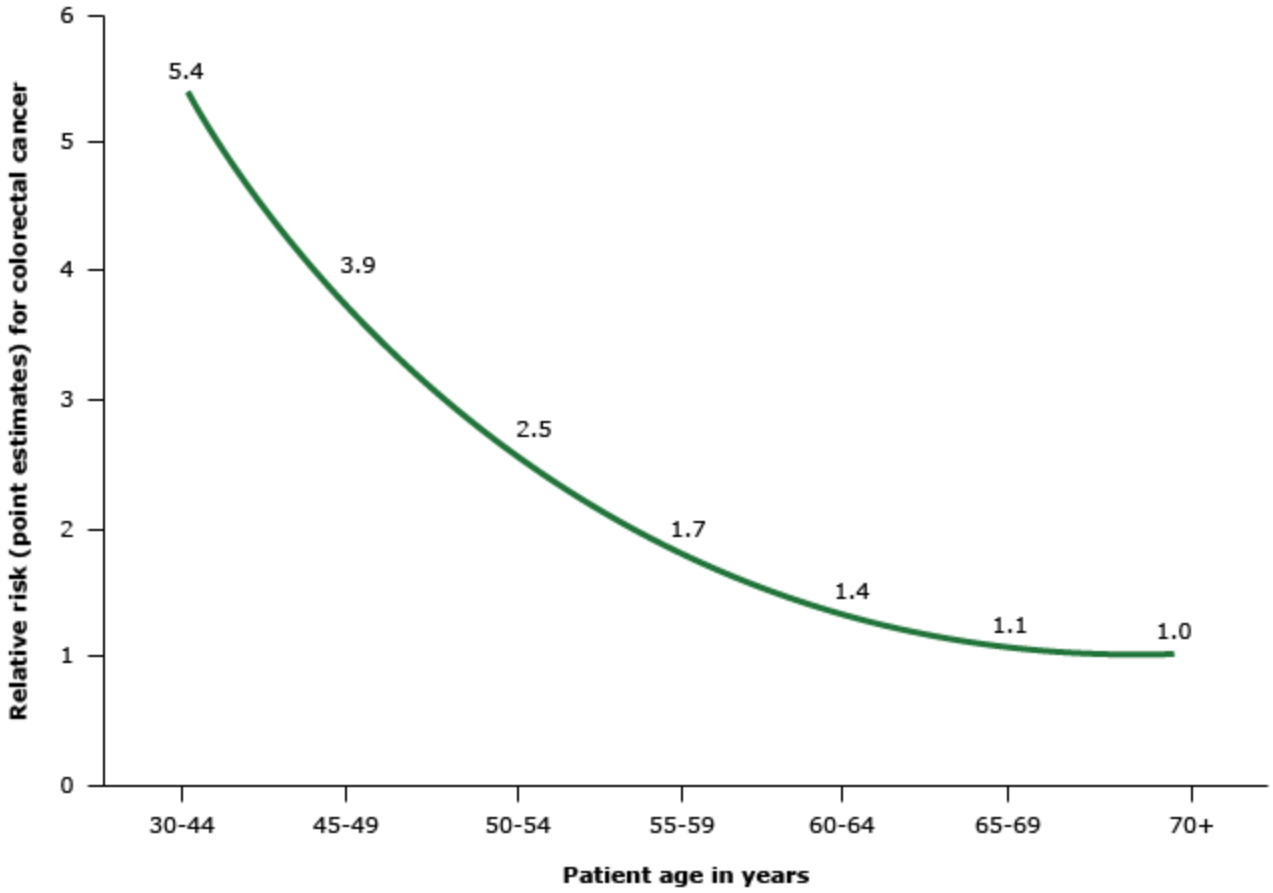


Graphic representation of the cumulative incidence of colorectal cancer demonstrates that in people with a family history, colorectal cancers occur earlier in life, not uncommonly in the 40s or even the 30s.

Data from Fuchs, CS, Giovannucci, EL, Colditz, GA, et al, N Engl J Med 1994; 331:1669.

Graphic 57102 Version 1.0

Risk of colorectal cancer associated with a first-degree relative with colorectal cancer, by patient age

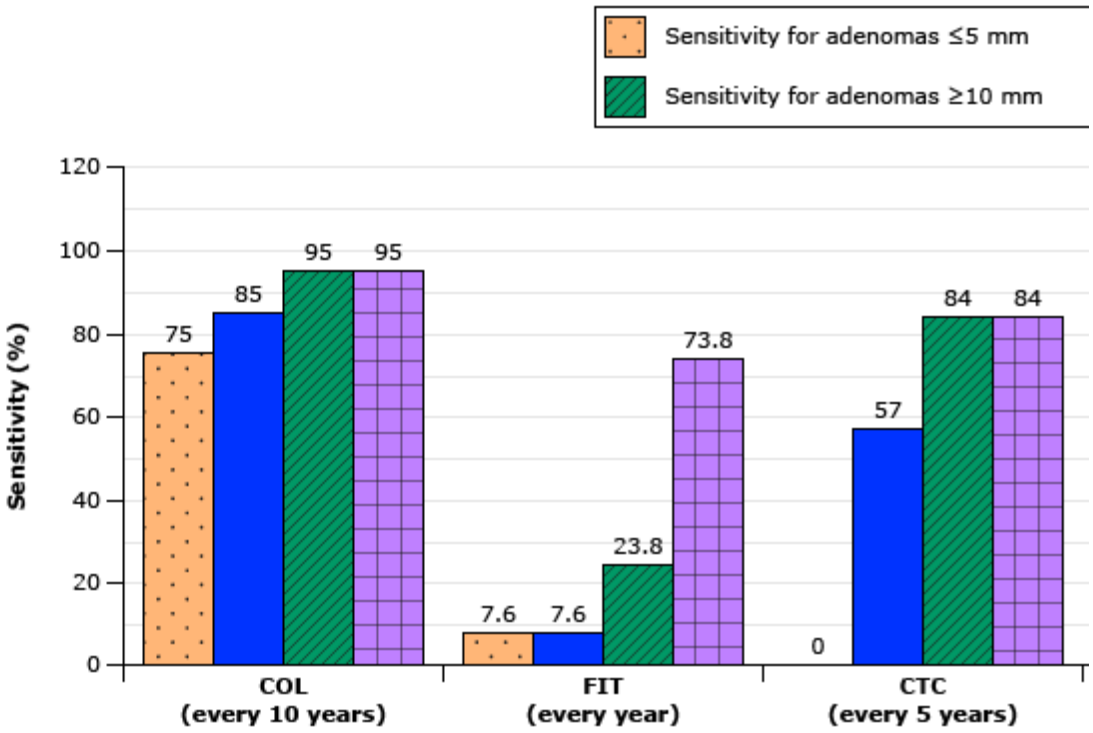


Data extrapolated from: Fuchs CS, Giovannucci EL, Colditz GA, et al. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994; 331:1669.

Numbers indicate point estimate reported for each age group.

Graphic 104863 Version 1.0

Estimated sensitivity, specificity, and cancer-specific deaths averted for each c



Test specificity	86	96.4	88
Colorectal cancer deaths averted per 1000 40-year-olds (n)*	22 to 24	20 to 23	16 to 24

Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

COL: colonoscopy; FIT: fecal immunochemical test; CTC: computed tomography colonography; SIG: sigmoid multitargeted stool DNA test.

* Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay

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Data from:

1. *Zauber A, Knudsen A, Rutter CM, et al. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collabor for Healthcare Research and Quality; October 2015.*
2. *Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies:*

Graphic 116366 Version 7.0

Contributor Disclosures

Scott D Ramsey, MD No relevant financial relationship(s) with ineligible companies to disclose. **William M Grady, MD** Grant/Research/Clinical Trial Support: PAVMed [Barrett's esophagus, esophageal cancer]. Consultant/Advisory Boards: DiaCarta [Colon cancer]; Freenome [Colon cancer]; GLG [Cancer, Gi disease]; Guardant Health [Colon cancer]; Guidepoint [Cancer, GI disease]; Helio [Liver cancer]; Natera [Colon cancer, multi-cancer early detection tests]; SEngine [Treatment response of cancer]. Other Financial Interest: Medscape [Colon cancer - Speaker]. All of the relevant financial relationships listed have been mitigated. **Joann G Elmore, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Jane Givens, MD, MSCE** No relevant financial relationship(s) with ineligible companies to disclose.

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