# Colorectal cancer: Epidemiology, risk factors, and protective factors

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## INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. The risk of developing CRC is influenced by both environmental and genetic factors. The epidemiology of CRC and risk factors for its development will be discussed here. Colorectal screening, clinical presentation, prognostic determinants, and treatment of colon and rectal cancer are discussed separately. (See "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp" and "Tests for screening for colorectal cancer" and "Screening for colorectal cancer: Strategies in patients at average risk" and "Clinical presentation, diagnosis, and staging of colorectal cancer" and "Pretreatment local staging evaluation for rectal cancer" and "Overview of the management of primary colon cancer" and "Adjuvant therapy for resected stage II colon cancer" and "Radical resection of rectal cancer" and "Surgical treatment of rectal cancer" and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy".)

## EPIDEMIOLOGY

CRC incidence and mortality rates vary markedly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, according to the World

Health Organization GLOBOCAN database [1]. Rates of both incidence and mortality are substantially higher in males than in females.

CRC incidence and mortality have been slowly but steadily decreasing in the United States [2]. Approximately 153,000 new cases of large bowel cancer are diagnosed annually, including about 107,000 cases of colon cancer and over 46,000 cases of rectal cancer [3]. Annually, over 52,500 people die of CRC in the United States.

**Incidence** — The regional incidence of CRC varies globally. The highest incidence rates are in Australia and New Zealand, Europe, and North America, and the lowest rates are found in Africa and South-Central Asia [4]. These geographic differences appear to be attributable to differences in dietary and environmental exposures, low socioeconomic status, and lower rates of CRC screening that are imposed upon a background of varying susceptibility [5-7].

In the United States, the lifetime incidence of CRC in patients at average risk is approximately 4 percent [3]. CRC incidence is approximately 33 percent higher in males than in females and is approximately 20 percent higher in Black Americans than in White Americans [3]. The incidence is higher in patients with specific inherited conditions that predispose them to the development of CRC. (See 'Risk factors' below.)

A gradual shift toward right-sided or proximal colon cancers has been observed both in the United States [8,9] and internationally [10,11] with the greatest relative increase in incidence in cecal primaries. This change in the anatomic distribution of CRCs may be, in part, related to improvements in diagnosis and treatment, and increased screening with removal of adenomatous polyps in the distal colon. Colonoscopy is more effective in preventing left-sided than right-sided CRCs, which could also contribute to a shift in distribution of cancers in the colon. It is likely that part of the difference is due to aspects of quality relating to the colonoscopy (poor right-sided preps, incomplete colonoscopy, anatomic configurations compromising visibility) but the biology may also differ between CRCs of the right and left colon. For example, serrated lesions, which are flatter and more difficult to visualize endoscopically, characteristically carry *BRAF* V600E mutations, give rise to microsatellite unstable CRCs, and are more common in the right colon. Although all of these issues may contribute to a shift toward right- rather than left-sided cancers, there also appears to be a true increase in the incidence of ascending colon and cecal cancers [11,12]. (See "Molecular genetics of colorectal cancer" and "Overview of colon polyps", section on 'Sessile serrated lesions' and "Tests for screening for colorectal cancer", section on 'Colonoscopy'.)

In the United States, CRC incidence rates had been declining by approximately 2 percent per year, but this rate of decline has slowed to approximately 1.2 percent per year in the period

2014 to 2018 [2]. Incidence rates in most other western countries have been stable or increased slightly during this period. By contrast, CRC incidence rates have rapidly increased in several areas historically at low risk, including Spain, and a number of countries within Eastern Asia and Eastern Europe [13,14].

**Age and early onset colorectal cancer** — Age is a major risk factor for sporadic CRC. Large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter ( figure 1).

Data from the United States Surveillance, Epidemiology, and End Results (SEER) database and other Western cancer registries suggest that CRC incidence is increasing in the under age 50 group while it is decreasing in older groups [15-24]. In the United States, the proportion of new CRC cases among adults under the age of 55 years increased from 11 to 20 percent between 1995 and 2019 [24]. Some registries report a rising incidence of CRC even among young adults up to 39 years of age, although the absolute number of cases in this age group remains far lower than for adults aged 50 or over [25-27].

These increases are being driven predominantly by left-sided cancers in general and rectal cancer in particular [20,24,28,29]. Over 86 percent of those diagnosed with CRC under the age of 50 are symptomatic, and the disease is being diagnosed at later stages, suggesting that the increased incidence is real and not representative of a shift in age at diagnosis attributable to earlier detection [18,30,31].

The reason(s) underlying this trend may be multifactorial, with contributions from genetic influences and changes in environmental and lifestyle exposures [32]:

- At least in the United States, it is estimated that up to 35 percent of these young adult cancers are associated with the known hereditary CRC syndromes, and the cause(s) for these increases remain unknown [28,29,33,34]. Interestingly, these trends have also been observed in lower middle-income countries traditionally thought of as having low rates of CRC compared with Western countries [1]. Literature suggests that ratios of early to late-onset CRC in multiple lower middle-income countries are strikingly higher than the international average in general and in the West in particular, although this may be partly due to the limited life expectancy of those populations [35].

  The high proportion of germline variants in these younger individuals emphasizes the importance of referral for genetic counseling and testing [36]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Indications for germline testing'.)

- A meta-analysis of 20 studies concluded that significant risk factors for early onset CRC (EOCRC) included CRC history in a first-degree relative (relative risk [RR] 4.21, 95% CI 2.61-6.79), hyperlipidemia (RR 1.62, 95% CI 1.22-2.13), obesity (RR 1.54, 95% CI 1.01-2.35), and alcohol consumption (RR for high versus nondrinkers 1.71, 95% CI 1.62-1.80) [37,38].

- Several other potential risk factors (eg, hypertension, metabolic syndrome, ulcerative colitis, chronic kidney disease, unhealthy dietary patterns [39-41], vitamin D intake [42], sedentary behavior, and occupational exposure to organic dusts) have only been examined in one or two studies. (See 'Obesity' below and 'Physical activity' below.)

- A pooled analysis of 13 population-based studies concluded that EOCRC was associated with not regularly using NSAIDs, greater red meat intake, lower educational attainment, alcohol abstinence, and heavier alcohol use [41]. However, no factors exhibited a greater excess in early-onset as compared with late-onset CRC.

- EOCRC has been associated with more advanced age-associated methylomic drift and accelerated aging in the normal mucosa of people with EOCRC, suggesting that drivers to methylation profiles characteristic of CRC are active earlier in EOCRC [43].

  However, others have failed to find any evidence that EOCRCs are clinically and genomically distinguishable from average-onset CRCs [29].

Current efforts to reduce young adult CRC incidence and mortality are focused on identifying those eligible for earlier age surveillance, based on family history, and promoting both clinician and consumer awareness of the potential cancer risk of symptoms, such as persistent rectal bleeding at any age [44].

The impact of these data on screening recommendations are discussed below.

**Mortality** — Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other western countries [2,3]. This improvement in outcome can be attributed, at least in part, to detection and removal of colonic polyps, detection of CRCs at an earlier stage, and more effective primary and adjuvant treatments. However, at least in the United States, the decline in CRC mortality started well before the widespread implementation of CRC screening and before effective adjuvant therapy became widely used [45]. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer" and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy".)

However, notably, in the United States the declining mortality overall is masking trends in younger adults:

- In data derived from the SEER Database of the National Cancer Institute, CRC mortality rates per 100,000 population among individuals under age 50 declined by approximately 2 percent per year from 2000 to 2004, and then increased by 1 percent annually through 2018. The increase was limited to White and Hispanic individuals; by contrast among Black individuals and Asian/Pacific Islander individuals, mortality rates were either stable or declined over this same time period [46].

- Similar trends are reported by the American Cancer Society [3,24], and the National Center for Health Statistics ( figure 2) [47].

Globally, the United States has one of the highest survival rates from CRC. Data collected by the SEER Program of the United States National Cancer Institute suggest that nearly 65 percent of all patients treated for CRC (all stages and sites combined) between 2011 and 2017 survive five years [48].

In contrast to these data, mortality rates continue to increase in many countries with more limited resources and health infrastructure, particularly in Central and South America and Eastern Europe, as reflected in data from the international WHO GLOBOCAN database [1].

## RISK FACTORS

Although data support the view that some risk factors are more related to colon than to rectal cancer [49], we will consider both entities together.

Environmental and genetic factors can increase the likelihood of developing CRC [50]. Although inherited susceptibility results in the most striking increases in risk, the majority of CRCs are sporadic rather than familial. These risk factors can be separated into those that confer a sufficiently high risk to alter recommendations for CRC screening, factors that may alter screening recommendations, and those that do not alter screening recommendations because they are thought to confer a small or uncertain magnitude of risk.

**Factors that currently influence screening recommendations** — CRC screening recommendations are modified for members of families with hereditary colon cancer syndromes, on the basis of personal or family history of CRC or adenomas, in patients with inflammatory bowel disease, and in those who have been exposed to abdominal radiation therapy.

**Hereditary CRC syndromes** — Several specific genetic disorders, most of which are inherited in an autosomal-dominant fashion, are associated with a very high risk of developing colon

cancer (see "Molecular genetics of colorectal cancer").

Familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) are the most common of the familial colon cancer syndromes, but together these two conditions account for only approximately 5 percent of CRC cases, the majority of which are Lynch syndrome [51-54]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of familial adenomatous polyposis".)

As many as 12 percent of unselected patients with CRC carry one or more pathogenic mutations in cancer-predisposing genes, and the majority of these are not Lynch syndrome or FAP [54]. In this analysis of 1058 individuals with CRC attending a tertiary American Cancer Center, 105 patients had one or more pathogenic mutations. Seventy-four (7 percent of the total) carried non-Lynch syndrome mutations, which included mutations in high-penetrance genes (*APC*, biallelic *MUTYH*, *BRCA1* and *BRCA2*, *PALB2*, *CDKN2A*, and *TP53*), as well as moderate-penetrance genes (monoallelic *MUTYH* [55], *APC* allele p.I1307K [56], *CHEK2*) for which the risk of CRC is not well defined. Broadening the approach, universal genetic testing yielded 6.4 percent more clinically actionable pathogenic germline variants in a series of patients presenting with solid tumors, many of whom had CRC [57]. With the falling costs of genetic testing, the reach of genetic testing is likely to extend further.

An even higher proportion (16 percent) of early onset CRCs (ie, diagnosed prior to age 50) may be associated with an inherited syndrome [58]. Furthermore, one-third of those found to have a potentially pathogenic germline mutation did not meet established genetic testing criteria for the gene in which they had a mutation. These data suggest that genetic counseling and testing with a multigene panel could be considered for all patients with early onset CRC.

### Adenomatous polyposis syndromes

**FAP** — Familial adenomatous polyposis (FAP) and its variants (Gardner syndrome, Turcot syndrome, and attenuated familial adenomatous polyposis [AFAP]) account for less than 1 percent of CRCs. In typical FAP, numerous colonic adenomas appear during childhood. Symptoms appear at an average age of approximately 16 years and colonic cancer occurs in 90 percent of untreated individuals by age 45 ( picture 1 and picture 2). AFAP carries a high risk of colon cancer (though its magnitude is not as well defined), but is characterized by fewer adenomas and an older average age of cancer diagnosis of 54 years. Clinical experience suggests less discrimination between FAP and AFAP, as there can be age-matched individuals with thousands of adenomas as well as those with oligo-polyposis within the same family. (See

"Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Attenuated FAP'.)

FAP is caused by germline mutations in the adenomatous polyposis coli (*APC*) gene which is located on chromosome 5. The same gene is involved in the attenuated form of FAP, but the sites of the *APC* gene mutations are different. (See "Molecular genetics of colorectal cancer" and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Familial adenomatous polyposis: Screening and management of patients and families".)

An *APC* gene variant occurring in approximately 6 to 8 percent of the Ashkenazi Jewish population has been associated with a 1.5- to 2-fold increased colon cancer risk without an associated polyposis [56,59]. However, in itself, it does not add risk beyond that of a family history in first-degree relatives and is therefore of limited clinical utility.

**MAP** — MUTYH-associated polyposis (MAP) is an autosomal-recessive syndrome due to biallelic germline mutations in the base excision repair gene mutY homolog (*MUTYH*). The phenotype of MAP is variable, but it can present with a polyposis phenotype; typically with fewer than 500 adenomas. The base excision repair system repairs mutations due to oxidative DNA damage, and the *APC* gene appears to be particularly susceptible to such damage. Thus, failure of the base excision repair system often leads to somatic mutations in *APC* and *KRAS*, especially G:C to T:A transversions, which can lead to a polyposis phenotype. An increasing number of reports suggest that germline mutations in these *MUTYH* genes may account for a substantial fraction of familial CRCs that occur in the absence of a dominantly inherited familial syndrome, and that a significant number of biallelic carriers present with cancer without associated polyposis, making their phenotype very difficult to identify. (See "Molecular genetics of colorectal cancer", section on 'MUTYH defects and familial colorectal cancer' and "*MUTYH*-associated polyposis".)

Other polyposis genes (*POLE* and *POLD1*, *MSH3*, and *NTHL*-associated polyposis [NAP]) are also part of next-generation panels with developing experience of their phenotypes. Pathogenic variants in *MSH3* and *NTHL*-associated polyposis are both inherited in an autosomal recessive manner.

**Lynch syndrome** — Lynch syndrome or HNPCC is an autosomal-dominant syndrome that is more common than FAP and accounts for approximately 3 percent of all colonic adenocarcinomas. Lynch syndrome can be suspected on the basis of a strong family history of CRC, endometrial, and other cancers. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Colonic manifestations'.)

The name Lynch syndrome honors the pioneering work of Dr. Henry Lynch in drawing attention to the syndrome. The term Lynch syndrome is now commonly reserved for families who have been genetically determined to have a disease-causing defect in one of the DNA mismatch repair (MMR) genes, most commonly *hMLH1*, *hMSH2*, *hMSH6*, or *hPMS2*. As a general rule, patients with Lynch syndrome have a germline mutation in one allele of an MMR gene, and the second allele is somatically inactivated in the CRCs by mutation, loss of heterozygosity, or, less commonly, epigenetic silencing by promoter hypermethylation. As a result, Lynch syndrome CRCs have impaired DNA MMR, are hypermutable, and are microsatellite unstable. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Colonic manifestations'.)

The colorectal tumors that develop in patients with Lynch syndrome are characterized by early age of onset and a predominance of right-sided lesions. The mean age at initial cancer diagnosis is approximately 48 years, with some patients presenting in their 20s. Nearly 70 percent of first lesions arise proximal to the splenic flexure, and approximately 10 percent will have synchronous (simultaneous onset of two or more distinct tumors) or metachronous cancers (non-anastomotic new tumors developing at least six months after the initial diagnosis). The chance of developing metachronous CRC in those who have had a segmental resection is high: in a study of 382 gene carriers, 16 percent at 10 years, rising to 62 percent at 30 years after primary resection [60].

Extracolonic cancers are very common in Lynch syndrome, particularly endometrial carcinoma, which may occur in up to 60 percent of female mutation carriers in some families. Other sites at increased risk of neoplasm formation include the ovary, stomach, small bowel, hepatobiliary system, brain and renal pelvis or ureter, and possibly breast and prostate.

Penetrance estimates for colon and endometrial cancer in carriers of *MLH1* or *MSH2* mutations were initially thought to be >80 percent, and 40 percent, respectively. However, these early estimates were based on selected families referred for gene testing, which produced biased estimates (upwards). Population-based series suggest that penetrance estimates are approximately one-half of what they were initially thought to be, and indicate that at least for carriers of an *MLH1* or *MSH2* mutation, the risk is highest in individuals aged 30 to 39, and that much of the risk attributed to this syndrome is over by the mid-50s [61]. Penetrance estimates for *MSH6* and *PMS2* carriers are even more modest, making identification of families with these genetic mutations more difficult to identify from family history interrogation [62]. *MSH6* carriers have a predilection for endometrial cancers. A clinically useful interactive database predicting future risk by gene, sex, age, and organ has been developed [63]. (See "Lynch syndrome

(hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

**Are patients with HBOC syndrome at risk?** — The majority of patients with hereditary breast and ovarian cancer (HBOC) syndrome have mutations in either the breast cancer type 1 or 2 susceptibility gene (*BRCA1* and *BRCA2*). HBOCs attributable to pathogenic variants in *BRCA* are characterized by an autosomal-dominant pattern of inheritance; markedly increased susceptibility to breast and ovarian cancers, with an especially early onset of breast cancer; and an increased incidence of tumors of other organs, such as the fallopian tubes, prostate, male breast, and pancreas. (See "Cancer risks and management of BRCA1/2 carriers without cancer".)

The biologic relationship between inherited *BRCA* gene mutations and CRC is unclear. Although some studies derived from a cancer risk clinic and the Breast Cancer Linkage Consortium have reported an approximately twofold increased risk of colon cancer among *BRCA1* mutation carriers [64-66], other population-based series have not confirmed such an association [67,68].

Two meta-analyses have come to different conclusions:

- One meta-analysis of 18 cohort and case-control studies concluded that carriers of *BRCA1* have a higher risk for CRC (odds ratio [OR] 1.49, 95% CI 1.14-1.85) [69]. There were no data on the age of onset of the CRCs in this analysis (although two of the included studies did report a higher risk for early onset CRC [66,70]). The study was also criticized for including family members of *BRCA* carriers with unknown mutation status; when the analysis was restricted to confirmed *BRCA1/2* mutation carriers, the risk was no longer statistically significant [71].

- A second meta-analysis of *BRCA* mutation carriers (seven cohort, four case-control studies, 14,252 carriers, with 4831 CRCs identified) failed to find an association between *BRCA1/2* mutation carriage and a higher risk for CRC (OR 1.03, 95% CI 0.80-1.32) [72]. Adjustment for age did not alter the outcome. Subgroup analysis also showed no significant increased odds of CRC in *BRCA1* carriers (OR 1.27, 95% CI 0.91-1.76), or in those with Ashkenazi Jewish heritage (OR 0.97, 95% CI 0.63-1.48).

There are no formal guidelines as to whether or not mutation *BRCA* carriers should initiate CRC screening at an earlier age than is typically recommended. Nevertheless, in our view, there are insufficient data on CRC risk to justify modifying screening guidelines for *BRCA* carriers. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Other solid tumors'.)

**Personal or family history of sporadic CRCs or adenomatous polyps** — Patients with a personal history of CRC or adenomatous polyps of the colon are at risk for the future development of colon cancer. In patients undergoing resection of a single CRC, metachronous primary cancers develop in 1.5 to 3 percent of patients in the first five years postoperatively. (See "Post-treatment surveillance after colorectal cancer treatment".)

A personal history of large (>1 cm) adenomatous polyps and polyps with villous or tubulovillous histology or with high-grade dysplasia also increases the risk of CRC, particularly if there are multiple polyps [73]. The relative risk (RR) ranges from approximately 3.5 to 6.5 in such patients. On the other hand, as a group, patients with one or two small (<1 cm) tubular adenomas with only low-grade dysplasia do not appear to be at substantially increased risk for subsequent CRC [73]. Recommendations are to manage these latter patients as average-risk individuals.

Family history is also an important risk factor even outside of the syndromes with a defined genetic predisposition. Having a single affected first-degree relative (parent, sibling, or child) with CRC increases the risk approximately twofold over that of the general population [74]. Risk is further increased if two first, or one first and one or more first or second-degree relatives on either side of the family have colon cancer, or if a first-degree relative is diagnosed below 50 years of age [75,76].

Patients who have a family member with an adenomatous colonic polyp may also be at increased risk for adenomas or cancer [74,77-80]. Some United States guidelines recommend earlier screening (age 40 years) for people with a family history of adenomas in relatives <60 years old or two first-degree relatives regardless of age [81-83], while others limit the recommendation to relatives of those with advanced adenomas [84]. A series from Hong Kong identifying an elevated risk for advanced adenomas in relatives of patients themselves with advanced adenomas supports screening in this group of relatives [85]. Guidelines in other countries (eg, Canada and Australia) do not recommend screening of relatives with adenomas, apart from the multiple polyposis syndromes [86,87]. (See "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp", section on 'Family polyp history'.)

In countries where screening is recommended for relatives of adenoma patients, we suggest that patients whose only familial risk factor for CRC is a relative with a history of adenomatous polyp that is not clearly documented as an advanced adenoma (≥1 cm, or high-grade dysplasia or villous elements) be screened as average-risk patients, with screening options presented separately. Individuals who have a first-degree relative with a documented history of advanced adenoma should be screened similarly to those with a family history of CRC. (See "Screening for colorectal cancer: Strategies in patients at average risk", section on 'Choosing a screening test'

and "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp", section on 'Family polyp history'.)

### Inflammatory bowel disease

**Ulcerative colitis** — There is a well-documented association between chronic ulcerative colitis and colonic neoplasia, with the extent, duration, and activity of disease being the primary determinants. Pancolitis confers a 5- to 15-fold increase in risk compared with the expected incidence in the general population, while disease that is limited to the left side of the colon is associated with approximately a threefold RR; in comparison, the risk does not appear to be significantly increased with proctitis or proctosigmoiditis alone [88,89]. There is evidence that some treatments for inflammatory colitis may decrease CRC risk and quiescent disease carries less risk than chronically active disease, justifying a reduction in frequency of surveillance [90]. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)

A reasonable estimate of the colon cancer incidence is approximately 0.5 percent per year for subjects with disease duration between 10 and 20 years, then 1 percent per year thereafter. Most reports suggest that the co-occurrence of ulcerative colitis and primary sclerosing cholangitis identifies a subset of patients with an even greater risk. Others have identified the presence of pseudopolyps as an independent risk factor, particularly if large and complex. Strictures should always raise a suspicion of malignancy. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Ulcerative colitis' and "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer" and "Overview of colon polyps", section on 'Inflammatory pseudopolyps'.)

The increase in risk of colon cancer begins approximately 8 to 10 years after the initial diagnosis of pancolitis, and at 15 to 20 years for colitis limited to the left colon ( image 1). The probability of developing cancer then increases with disease duration and in those with active inflammation; by the fourth decade of disease it reaches as high as 30 percent in patients with pancolitis. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Extensive colitis'.)

**Crohn disease** — Although there are much less data, it appears that pancolitis due to Crohn disease is associated with a similar RR of colon malignancy as extensive ulcerative colitis, although the data are less consistent. Recommendations from expert groups vary for Crohn disease where there is less colonic involvement, but most guidelines recommend surveillance when one-third or more of the colonic mucosa is involved. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Crohn disease'.)

**Abdominopelvic radiation** — Cancer survivors who received abdominopelvic radiation therapy in childhood or as adults are at significantly increased risk of subsequent gastrointestinal neoplasms, the majority being CRC [91-93].

For adult survivors of pediatric cancer, there is no consensus as to the optimal time to start screening and the optimal interval between screening evaluations. Guidelines from the Children's Oncology Group recommend colonoscopy every five years for survivors of childhood cancer who received abdominal, pelvic, spine, or total-body irradiation, with screening beginning five years after radiation therapy or at age 30 years, whichever occurs later [94]. Screening options include colonoscopy every five years (preferred) or multitarget stool DNA test every three years. Others suggest screening every 10 years from age 40 to 60 years as a more cost-effective strategy [95]. Guidelines from expert groups outside of the United States do not specify the time to the start of the screening strategy either [96-98].

A history of radiation therapy for prostate cancer has been associated with an increased risk of rectal cancer in two large database studies [99,100]. The magnitude of risk is approximately similar to that observed in patients with a family history of colonic adenomas. Whether such cancers follow an adenoma to cancer sequence, and whether increased screening in such patients would improve cancer detection rates and outcomes, is unclear. In contrast to adult survivors of childhood cancer, increased surveillance is not currently recommended in this group.

**Cystic fibrosis** — Patients with cystic fibrosis (CF) have an elevated risk of CRC. In a meta-analysis, the pooled standardized incidence ratio was 10.91, 95% CI 8.42-14.11, and it was two- to fivefold higher following lung transplantation [101]. The Cystic Fibrosis Foundation (CFF) has developed guidelines for CRC screening for adults with CF. Although risk estimates are provided, the benefits of screening for CRC in these patients, who as a group have substantial comorbidities, are less certain. This subject is discussed in more detail separately. (See "Cystic fibrosis: Overview of gastrointestinal disease", section on 'Gastrointestinal cancer'.)

**Factors that may influence screening recommendations**

**Age** — The rising incidence of early onset CRC, particularly among those in the 40 to 49 year old age group, has prompted at least two groups to lower the recommended age of first screening (see 'Age and early onset colorectal cancer' above):

- In 2018, the American Cancer Society issued a "qualified" recommendation to begin screening persons at average risk for CRC at age 45 years [102].

- In 2021, the United States Preventive Services Task Force changed its recommendation to include screening for CRC in adults starting at age 45 [103].

Other expert groups have not yet changed their recommendations [104-106]. Screening for CRC is discussed in detail separately. (See "Screening for colorectal cancer: Strategies in patients at average risk" and "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp".)

**Race and sex** — Black Americans, Native Americans, and Alaskan Native individuals have among the highest incidence and mortality rates for CRC of all racial and ethnic groups in the United States [24]. In addition, CRCs occur at a younger age, as there is a higher frequency of CRC under age 50 in these populations [107]. Among Black Americans, there also appears to be a more proximal distribution of both CRCs and adenomas. The reasons for these findings are unclear, but may be related to a higher prevalence of risk factors associated with CRC and lower rates of access to screening among these populations.

Screening strategies do not differ with regard to race. (See "Screening for colorectal cancer: Strategies in patients at average risk".)

CRC mortality is approximately 33 percent higher in males than in females [24]. Both colonic adenomas and CRCs appear to have a more proximal distribution in females [108], particularly in postmenopausal females. None of the major United States organizations recommend that screening be stratified by sex, but some authors have argued that this should be considered [109], or that flexible sigmoidoscopy is an inadequate screening test in females [108].

**Acromegaly** — Most reports suggest that colonic adenomas and CRC both occur with increased frequency in acromegaly [110,111], particularly in those with uncontrolled disease.

Guidelines from the Acromegaly Consensus Group recommend colonoscopy for early detection and treatment of premalignant colonic polyps at the time of diagnosis [112]. (See "Causes and clinical manifestations of acromegaly", section on 'Colonic effects'.)

**Renal transplantation** — Renal transplantation, in association with long-term immunosuppression, has been linked with increased CRC risk [113,114]. In general, cancer rates in kidney transplant recipients are similar to those of non-transplanted individuals 20 to 30 years older [114]. However, many renal transplant recipients have comorbidities that need to play into screening decisions for CRC. (See "Malignancy after solid organ transplantation".)

**Risk factors that do not alter screening recommendations** — There are a large number of clinical environmental and lifestyle factors that are associated with a small and/or uncertain

increased risk of CRC. Although many of these associations have been seen consistently in observational studies, the causal relationship of these associations is largely unproven. Patients may be counseled about these associations and encouraged to reduce or avoid such factors for the primary prevention of CRC.

**Obesity** — Obesity is a risk factor for CRC [115,116]. A systematic review and meta-analysis of data from 13 studies reported that a weight gain between early adulthood and midlife was associated with a modest but significant increase in the risk of CRC (hazard ratio [HR] 1.23, 95% CI 1.14-1.34) [115]. The HR for weight gain between midlife and older adulthood was lower, but still statistically significant (HR 1.15, 95% CI 1.08-1.24). The risk was highest for those in the highest weight gain category. Obesity also appears to increase the likelihood of dying from CRC. (See "The roles of diet, physical activity, and body weight in cancer survivors" and "Overweight and obesity in adults: Health consequences", section on 'Cancer' and "Adjunctive therapy for patients with resected early stage colorectal cancer: Diet, exercise, NSAIDs, and vitamin D", section on 'Diet and exercise'.)

The excess risk associated with obesity is reduced after bariatric surgery, with at least one report suggesting that CRC rates approximate those in the general population within five or six years of surgery [117,118]. (See "Bariatric surgery for management of obesity: Indications and preoperative preparation" and "Outcomes of bariatric surgery".)

**Diabetes mellitus and insulin resistance** — Diabetes mellitus is associated with an elevated risk of CRC [119-129]. A meta-analysis of 14 studies (6 case-control and 8 cohort) estimated that the risk of colon cancer among diabetics was approximately 38 percent higher than nondiabetics (RR 1.38, 95% CI 1.26-1.51), and for rectal cancer it was 20 percent higher (RR 1.20, 95% CI 1.09-1.31) [126]. The associations remained when the analysis was limited to studies that controlled for smoking, obesity, and physical activity. This level of increased risk is insufficient to influence surveillance recommendations based upon other factors such as age.

One possible explanation linking diabetes to CRC is hyperinsulinemia, because insulin is an important growth factor for colonic mucosal cells and stimulates colonic tumor cells [130-132]. Plasma concentrations of insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFBP-3) were reported to influence the risk of CRC in a cohort of 14,916 males who were followed prospectively [133]. Subjects with values of IGF-1 in the highest quintiles were more likely to develop CRC compared with those with values in the lowest quintiles (RR 2.51).

In addition to increasing risk of the disease, diabetes may also influence prognosis among patients with CRC [134,135]. As an example, in one cohort study of patients with non-metastatic CRC who were enrolled in the Cancer Prevention Study-II Nutrition Cohort, individuals with type

2 diabetes mellitus had a significantly higher risk of cancer-specific mortality relative to those without diabetes [134]. The association was not related to insulin levels as use of insulin did not influence CRC mortality.

**Red and processed meat** — Although the data are not entirely consistent, long-term consumption of red meat or processed meats appears to be associated with an increased risk of CRC, particularly for left-sided tumors [136-140]. High temperature cooking (eg, barbecuing, pan-frying) has been implicated as contributing to risk, perhaps by the production of polyaromatic hydrocarbons and other carcinogens produced from proteins in the charring process. Lean red meat may be associated with less risk [141].

In 2015, the World Health Organization's International Agency for Research on Cancer (IARC) reviewed the evidence linking intake of red and processed meat with CRC; they classified consumption of processed meat as carcinogenic to humans and consumption of red meat as probably carcinogenic [142]; this position was reiterated in its 2020 report [143]. In 2018, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) similarly concluded that the evidence was convincing that consumption of processed meat increases risk of CRC, whereas the evidence for consumption of unprocessed red meat was classified as probable. It is estimated that for every 50 grams of processed meat consumed per day, the risk of CRC increases by approximately 16 percent, and for every 100 grams of red meat consumed per day, it increases by approximately 12 percent [143]. For colon cancer, these estimates were 23 and 22 percent, respectively.

Based upon the large amount of data and the consistent association of CRC with processed meats across studies in different populations, which make chance, bias, and confounding unlikely as explanations, the IARC concluded that there was sufficient evidence in human beings to classify processed meats (eg, sausages, bacon, ham, beef jerky, corned beef, and other smoked, salted, fermented, or cured meats) as group 1 carcinogens, placing these foods in the same risk category for cancer as asbestos, cigarettes, and alcohol (although the amount of increased risk is nowhere near the same) [142,143].

Chance, bias, and confounding could not be ruled out with the same degree of confidence for the data on red meat consumption, since no clear association was seen in several high-quality studies, and residual confounding from other diet and lifestyle factors was difficult to exclude. Nevertheless, the working group concluded that there is limited evidence in human beings for the carcinogenicity of consuming red meat (ie, beef, pork, lamb, veal, mutton, horse, goat) and classified these foods as group 2A carcinogens (probably associated). Other dietary guidelines also support limiting consumption of red and processed meat [144].

However, these conclusions are based entirely on observational studies. It is important to note that data from at least two randomized trials are not consistent with the hypothesis that red and/or processed meat consumption increases the risk of colorectal neoplasia [145]. As an example, the Women's Health Initiative, which involved almost 50,000 females, was unable to show that a reduction in dietary fat, including animal fat, reduced risk of CRC after more than eight years of follow-up [146]. (See "Dietary fat", section on 'Cancer'.)

Furthermore, at least some data suggest that the association between consumption of processed meat and risk of CRC may be modified by inherited susceptibility [147].

In 2019, dietary recommendations proposed by the Nutritional Recommendations Consortium (NutriRECS) indicated that prior recommendations that adults reduce their current red and processed meat consumption to reduce their risk of CRC were not supported by their analysis [148]. Their recommendation was based on four meta-analyses showing low-certainty evidence of the very small adverse health effects of red and processed meat consumption [149-152] and a systematic review evaluating consumer values and preferences [153]. It is unclear where these recommendations should fit in relation to those of other groups that support limiting consumption of red and processed meats [142,144]. While the findings of their meta-analyses were actually similar to others', their use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which classifies all observational data as low-quality evidence, remains a point of contention.

Overall, although there may be an increased risk of developing CRC associated with intake of processed meats, the absolute risk is small and only occurs with daily consumption, and it is not clear that all individuals have the same risk. In our view, modest consumption of red and/or processed meat (one to two times weekly at most) is an acceptable part of a healthy, balanced diet. (See "Healthy diet in adults".)

**Tobacco** — Cigarette smoking has been associated with increased incidence and mortality from CRC. A meta-analysis of 106 observational studies estimated that the risk of developing CRC was increased among cigarette smokers compared with those who never smoked (RR 1.18, 95% CI 1.11-1.25) [154]. The risk of dying from CRC was also increased among smokers (RR 1.25, 95% CI 1.14-1.37). For both incidence and mortality, the association was stronger for cancer of the rectum than the colon.

Cigarette smoking is also a risk factor for essentially all types of colonic polyps. For adenomatous polyps, the risk is particularly high for more advanced adenomas (ie, larger and with severely dysplastic features) [155]. Smoking is also a risk factor for serrated polyps of the

colon, including those that are hyperplastic and those that are with dysplasia [156,157]. In addition, smoking may increase the risk of CRC in patients with Lynch syndrome (HNPCC) [158].

For these and a host of other reasons, smoking should be avoided, especially by CRC survivors. (See "Approach to the long-term survivor of colorectal cancer", section on 'Alcohol and tobacco use'.)

**Alcohol** — An association between alcohol consumption and an increased risk of CRC has been observed in several studies. A meta-analysis of 27 cohort and 34 case-control studies concluded that, compared with never drinkers, there was a significant increase in risk of CRC for moderate (two to three drinks per day, summary RR 1.21, 95% CI 1.13-1.28) and heavy drinkers (≥4 drinks per day, RR 1.52, 95% CI 1.27-1.81), but not light drinkers (≤1 drink per day, RR 1.00, 95% CI 0.95-1.05) [159]. These results are consistent with other pooled analyses [160-162]. However, in contrast to prior studies, a dose-response analysis found a significant 7 percent increase in risk of CRC even in light drinkers (RR for ingestion of 10 g/day of ethanol 1.07 [95% CI 1.04-1.10]). The elevated risk may be related to interference of folate absorption by alcohol and decreased folate intake [163,164]. (See "Overview of the risks and benefits of alcohol consumption".)

Excessive alcohol consumption is an established, potentially modifiable risk factor for several other malignancies in addition to CRC [143,165], and it also complicates treatment and treatment outcomes by contributing to longer hospitalizations, prolonged recovery, higher health care costs, and greater overall and cancer-related mortality. The American Society of Clinical Oncology (ASCO) has issued a statement on the association of alcohol consumption with multiple cancers, which outlines proposals for promoting awareness of the association between alcohol abuse and certain types of cancer, supporting policy efforts to reduce the risk of cancer through evidence-based strategies that prevent excessive use of alcohol, and providing education to oncology providers about the influence of excessive alcohol use on cancer risk and treatment complications [166].

**Use of androgen deprivation therapy** — A review of 107,859 males aged 67 and older with prostate cancer who were included in the linked Surveillance, Epidemiology, and End Results Reporting (SEER)/Medicare database suggests that long-term androgen deprivation therapy (ADT) may also increase the risk of CRC [167]. Males who received treatment with a gonadotropin-releasing hormone (GnRH) agonist or orchidectomy had a higher risk of developing CRC, and the risk increased with longer duration of ADT. Compared with no ADT, the HR for CRC associated with a GnRH agonist for 25 months or longer was 1.31 (95% CI 1.12 to 1.53), and for orchidectomy it was 1.37 (95% CI 1.14-1.66). The mechanism(s) underlying this putative association are unclear, but insulin resistance as a consequence of ADT has been

suggested as a possible contributor [168]. These risk estimates fall below those qualifying for special attention in most screening guidelines.

**Cholecystectomy** — A relationship between cholecystectomy and right-sided colon cancer has been described in some reports. As an example, in a study of 278,460 patients followed for up to 33 years after surgery, patients who had undergone cholecystectomy had a slightly increased risk of right-sided colon cancer (standardized incidence ratio 1.16), but not more distal colon cancers [169]. Several meta-analyses have confirmed this association with proximal colon cancers [170,171], although discordant data have also been reported [172,173]. The mechanism is thought to be related to alterations in bile acid composition in the colon after cholecystectomy [174-176].

**Other risk factors** — Several other risk factors have been studied:

- The presence of coronary heart disease has been associated with an increased risk of CRC and advanced adenomas [177]. The mechanisms underlying the association are unclear but may be related to shared risk factors.

- Ureterocolic anastomoses after extensive bladder surgery are associated with an increased risk of neoplasia in close proximity to the ureteric stoma [178]. (See "Urinary diversion and reconstruction following cystectomy", section on 'Ileal conduits'.)

- A cohort study from the Manitoba Cancer Registry suggests that young females (50 years or younger) with endometrial cancer are at a four- to fivefold higher chance of developing CRC (particularly right-sided tumors) than the general population [179]. Although previous studies of this question have been inconsistent and this study did not address the contribution of Lynch syndrome to their analyses, it does suggest that females with young-onset endometrial cancer should be screened for Lynch syndrome and considered for colonoscopic screening at or around the time of diagnosis of endometrial cancer.

- Several bacterial and viral agents (eg, *Streptococcus bovis*, *Helicobacter pylori*, JC virus, human papilloma virus [HPV], *Fusobacterium nucleatum*, colonization of the gut by pathogenic strains of *E. coli* with associated production of colibactin, a DNA-damaging metabolite, and decreased diversity of the gut bacterial microbiome) have been proposed as risk factors for CRC [180-191]. Some data suggest a potential role for intestinal microbiota in mediating the association between diet and colorectal neoplasia [192]. (See 'Fiber' below.)

  In support of the possibility that alterations in the gut microbiome influence risk, at least some data suggest an association between antibiotic use and colorectal neoplasia,

although causality remains uncertain [193,194]. One of the ways in which the gut microbiome might influence colorectal neoplasia is through altering the bioavailability of aspirin [195]. (See 'Aspirin and NSAIDs' below.)

An association between *H. pylori* infection and colorectal polyps and CRC has been described but remains controversial [180,196,197]. The data linking JC virus infection to CRC have been mixed and inconclusive [180]. The association between infection with *S. bovis*, particularly the *S. gallolyticus* subtype [198], and colonic neoplasia is well described, but is thought to be a consequence of, rather than a risk factor for, colonic neoplasia and is discussed separately. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy", section on 'Colon cancer' and "Infections due to Streptococcus bovis/Streptococcus equinus complex (SBSEC; formerly group D streptococci)" and "Infections due to Streptococcus bovis/Streptococcus equinus complex (SBSEC; formerly group D streptococci)", section on 'Association with colonic neoplasia'.)

- Several (but not all [199]) studies suggest that prolonged sitting, independent of physical inactivity and obesity, increases the risk of CRC, particularly young-onset CRC [200-202]. (See 'Incidence' above.)

## PROTECTIVE FACTORS

A large number of factors have been reported by at least some studies to be associated with a decreased risk of CRC [203]. These include regular physical activity, a variety of dietary factors, the regular use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone replacement therapy in postmenopausal females. None of these factors is currently used to stratify CRC screening recommendations.

**Physical activity** — Substantial observational data and several systematic reviews have concluded that regular physical activity, either occupational or leisure time, is associated with protection from CRC [204-209]. In a meta-analysis of 21 studies, there was a significant 27 percent reduced risk of proximal colon cancer when comparing the most versus the least active individuals (relative risk [RR] 0.73, 95% CI 0.66-0.81) [205] and a 26 percent reduction for distal colon cancer (RR 0.74, 95% CI 0.68-0.80). The mechanism underlying the apparent protective association of physical activity is not known and no intervention trials of physical activity for CRC prevention have been reported. (See "The benefits and risks of aerobic exercise", section on 'Cancer prevention and treatment'.)

**Diet** — Many epidemiologic studies have shown an association between the intake of a diet high in fruits and vegetables and protection from CRC [210-212]. The RR of CRC is approximately 0.5 comparing groups with the highest intake to those with the lowest [212]. However, discordant data have also been published. The link between consumption of produce and CRC was challenged in a prospective cohort study that combined subjects from the Nurses' Health Study (88,764 females) and the Health Professionals Follow-up Study (47,325 men) [213]. In that analysis, there was no significant association between the consumption of fruits, vegetables, or the combination on the incidence of either colon or rectal cancer, independent of vitamin supplement use or smoking habits.

A pooled analysis of fourteen cohort studies, including the previous study, concluded that eating more than 800 g fruit and vegetables daily, compared with less than 200 g, decreased risk for distal (RR 0.74) but not for proximal colon cancer [214]. On the other hand, a later meta-analysis of 19 cohort studies concluded that there was a weak protective effect of fruit and vegetable intake for highest versus lowest intake of fruits and vegetables (RR 0.92, 95% CI 0.86-0.99) and that the inverse association appeared limited to distal colon cancers [215]. Most of the risk reduction was attributable to increasing intake above a threshold value of 100 g/day, with relatively little benefit associated with higher levels of intake. As a reference, a typical apple weighs >200 g. These data suggest that there might be little benefit to increasing the consumption of fruits and vegetables beyond the levels associated with eating a reasonable balanced diet.

Compared with non-vegetarians, vegetarian dietary patterns have also been associated with a significantly reduced risk of CRC, with the effect being most pronounced among pesco-vegetarians [216,217].

**Fiber** — A number of laboratory, nutritional, and epidemiologic studies have identified a role for dietary fiber in the pathogenesis of CRC [218]. However, the degree to which dietary fiber protects against the development of adenomas or CRC is uncertain since the results of epidemiologic studies, randomized trials, and meta-analyses of prospective observational studies are discordant:

- A decreased risk of colonic adenomas and CRC with higher intake of fiber was reported in five large epidemiologic studies [219-223].
- On the other hand, in an analysis from the combined Nurses' Health Study and Health Professionals Follow-up Study, no relationship was noted between total dietary fiber intake and risk of CRC [224]. Similarly, the Women's Health Initiative Trial found no protective

effect of a modest low-fat, increased fiber, and increased fruit and vegetable dietary intervention on CRC incidence [146].

- A pooled analysis of 13 prospective cohort studies (involving 725,628 males and females followed for 6 to 20 years) found that dietary fiber intake was inversely associated with the risk of CRC, but the association was no longer apparent after accounting for other dietary risk factors [225].

- A meta-analysis funded by the World Cancer Research Fund found that for every 10 g/day increase in dietary fiber consumption, there was a significant reduction in the risk of CRC by 10 percent [226,227]. There was a difference between different food groups. While fiber from grains was associated with protection from CRC, fruit, vegetable and legume-based fiber was not. This conclusion was partially supported by a later case-control study nested within the European Prospective Investigation into Cancer and nutrition (EPIC) study, which found that high consumption of whole grains was associated with a lower rate of distal colon cancer development, but there was no association with overall CRC risk [228].

- In two randomized controlled studies from the United States as well as one from Australia, fiber supplementation had no significant protective effect for the development of total colorectal adenomas [141,229,230].

- A systematic review of five studies involving a total of 4349 patients concluded that there was no definitive evidence that increased dietary fiber reduces the incidence or recurrence of adenomatous polyps within a two- to four-year period [231].

While multiple potential explanations may account for the differences among studies [222,232], the type of fiber may be one important factor, as was found in the World Cancer Research Fund meta-analysis. In addition to this analysis, the Australian trial described above, which showed a significant reduction in advanced adenomas (only), used unprocessed wheat bran, which may be more effective in delivering the benefits of cereal fiber as compared with more processed forms [141]. Ultimately, the degree of protection from dietary fiber, if any, will likely remain unsettled in the absence of prospective intervention studies.

One intriguing study suggests an interaction between intestinal microbiota (particularly *Fusobacterium nucleatum*) and dietary intake of fiber in mediating the risk of colorectal neoplasia [192]. Bacteria like *F. nucleatum* appear to play a role in stimulating colorectal carcinogenesis, possibly through suppression of the host's immune response to the tumor [187,233]. (See 'Other risk factors' above.)

In this prospective cohort study using data from the Nurses' Health Study and the Health Professionals Follow-up Study, a total of 1019 incident colon and rectal cancer cases with available *F. nucleatum* data (using quantitative polymerase chain reaction) were documented over 26 to 32 years of follow-up [192]. Prudent diets rich in whole grains and dietary fiber were associated with a significantly lower risk for *F. nucleatum*-positive but not *F. nucleatum*-negative CRCs.

**Resistant starch** — Resistant starch refers to those forms of starch which escape digestion in the small bowel and pass to the colon, where they are fermented with the production of short-chain fatty acids. Butyrate, one of these fatty acids, has antineoplastic properties in the colon [234]. While this led to initial enthusiasm as to the potential of resistant starch as a chemopreventive agent, a randomized trial of resistant starch (Novelose, 30 g daily) failed to show a beneficial impact on adenoma or cancer development in individuals with Lynch syndrome. [235,236]. However, in long-term follow-up of this trial, resistant starch did provide a delayed protective effect on all non-colorectal Lynch syndrome cancers, especially those in the upper gastrointestinal tract [237]. Additional trials of other forms of resistant starch that are capable of delivering higher levels of butyrate to the colon are in progress.

**Folic acid and folate** — Folate is the natural form of the vitamin occurring in food, and folic acid is the synthetic form used in food fortification and supplements. Based upon biochemical pathways, the two may not be equivalent and have different in vitro effects.

Data from animal and human studies have demonstrated that folate inhibits pathogenesis of cancer in a number of tissues including the colon [238]. However, whether folate and folic acid have a role in prevention of CRC is unclear. By contrast, the possibility that folic acid supplementation **increases** the risk of colon cancer has also been raised. The following represents the available data on folate and CRC risk:

- A combined analysis of data from two large cohorts from the Nurses' Health Study and the Health Professionals Follow-up Study provide observational evidence in support of a protective effect from folic acid supplementation [239]. There was an association between total folate intake 12 to 16 years before diagnosis and a lower risk of CRC (RR 0.69; 95% CI 0.51-0.94 for ≥800 compared with <250 micrograms of folate per day), but no association with more recent intake. By contrast, both long- and short-term intake of total folate was associated with a lower risk of colorectal adenomas, with a strong association with intake four to eight years before diagnosis (OR 0.68; 95% CI 0.60-0.78 for ≥800 compared with <250 micrograms of folate per day). These observational data suggest that folic acid supplementation could be beneficial in the pre-adenoma stage but not beyond.

- In contrast to these data, at least two controlled trials involving patients with colonic adenomas found that folic acid supplementation did not reduce the risk of recurrent adenomas [240,241]. Furthermore, in one of the trials, supplementation was associated with an increased risk of having three or more adenomas and of non-CRCs, raising the possibility that folic acid supplementation in adults could be detrimental rather than beneficial for adenoma formation, particularly in those who already have a propensity to form colonic neoplasms [240,242]. An increased risk of colorectal neoplasia from folic acid supplementation or in patients with high plasma levels of unmetabolized folic acid (which accumulates if the body's capacity to reduce folic acid is exceeded) has not been confirmed by others [215,243,244].

**Vitamin B6 (pyridoxine)** — The available data suggest a modest association between higher vitamin B6 (pyridoxine) intake and decreased CRC risk. In a meta-analysis of prospective studies, the pooled RRs of CRC for the highest versus lowest categories of vitamin B6 intake and of blood levels of pyridoxal 5'-phosphate (the active form of vitamin B6) were 0.90 (95% CI 0.75-1.07) and 0.52 (95% CI 0.38-0.71), respectively [245]. Omitting one study that contributed substantially to heterogeneity in the studies of vitamin B6 intake, the protective effect of highest versus lowest vitamin B6 intake on CRC risk was statistically significant (pooled RR 0.80, 95% CI 0.69-0.92).

**Calcium and dairy products** — Another possible protective factor is increased intake of dietary or supplemental calcium [246-253].

At least three controlled trials have evaluated the efficacy of calcium supplementation in prevention of recurrence of colorectal adenomas. A meta-analysis of these data (including a total of 1485 subjects) concluded that the risk of recurrence was significantly lower in patients randomized to calcium (RR 0.80, 95% CI 0.68-0.93) [254].

Despite these benefits in adenoma prevention trials, whether calcium supplementation reduces the risk of CRC is unproven. The following data are available:

- A protective effect of higher calcium intake on the risk of CRC was suggested in an analysis of combined data from the Nurses' Health Study and the Health Professionals Follow-up Study [255]. Calcium intake was assessed every four years. Total calcium intake (≥1400 versus <600 mg/day) was associated with a statistically significant lower risk of colon cancer (multivariable RR 0.78, 95% CI 0.65-0.95).

- On the other hand, a large controlled trial of 36,282 postmenopausal females who were randomly assigned to the combination of calcium (1000 mg daily) plus vitamin D3 (400 units daily) or placebo showed no significant difference in the rate of invasive CRC during a

mean follow-up of seven years [256]. Questions have been raised as to whether the doses of calcium and vitamin D3 that were used in the trial were sufficient to prevent colon cancer.

However, a subsequent smaller trial of 2303 older females who were assigned to placebo or higher doses of calcium (1500 mg daily) and vitamin D3 (2000 international units daily) also failed to confirm a lower risk of invasive or in situ CRC in the supplemented group over four years [257].

- Finally, a post hoc analysis of a randomized controlled trial of calcium and vitamin D reported an increased risk of serrated polyps in those randomized to calcium (adjusted risk ratio 2.65, 95% CI 1.43-4.91) and calcium plus vitamin D (risk ratio 3.81, 95% CI 1.25-11.64) [258].

The protective effect of calcium on conventional adenomas may depend upon an individual's genotype for the vitamin D receptor [251] and/or on having normal levels of vitamin D [259].

Calcium supplementation has been recommended for the primary or secondary prevention of colonic adenomas by the American College of Gastroenterology [249]. (See "Overview of colon polyps".)

Epidemiologic studies of dairy products and CRC risk have provided mixed results, with some studies reporting inverse associations between intake of total dairy products, milk, and/or yogurt and CRC risk, and others finding no association. Dairy products have been hypothesized to protect against CRC because of their high calcium content; however, some dairy products, such as cheese and cream, have a high fat content, which may counterbalance the protective effect, possibly by affecting the bile acid composition in the colon. (See 'Cholecystectomy' above.)

A meta-analysis of 19 cohort studies concluded that diets with higher milk and total dairy product intake were associated with a significant, but modest, reduction in CRC risk (summary RR for milk 0.82, 95% CI 0.74-0.93) [260]. The protective effect was restricted to colon and not rectal cancer. There was no association between intake of cheese or other dairy products (including low-fat dairy products) and CRC risk.

**Vitamin D** — Vitamin D and its metabolites act as inhibitors of CRC progression in model systems by effects that influence both initiation and progression [261]. An analysis by the World Health Organization identified colon cancer as the type of cancer with the greatest risk associated with poor vitamin D status [262].

Observational studies also suggest an association between low vitamin D levels and the risk of many cancers, including CRC [263,264]. This association was demonstrated in a pooled analysis of 5706 patients with CRC and 7107 control patients with a range of circulating 25-hydroxyvitamin D (25(OH)D) levels [264]. Compared with 25(OH)D levels of 20 to <25 ng/mL, lower levels of 25(OH)D (<12 ng/mL) were associated with a higher risk of CRC (RR 1.31, 95% CI 1.05-1.62). In contrast, higher levels of 25(OH)D (≥30 ng/mL) were associated with a lower risk of CRC (RR 0.81, 95% CI 0.67-0.99 for levels of 30 to <35 ng/mL; RR 0.73, 95% CI 0.59-0.91 for levels of 35 to <40 ng/mL, respectively). These vitamin D levels (30 to 40 ng/mL [75 to 100 nmol/L]) are within the accepted range for optimizing skeletal health. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment", section on 'Serum 25-hydroxyvitamin D'.)

There are two caveats:

- It is not clear if these observed associations are causal as the current interventional data on the protective effect of vitamin D supplementation on the development of colorectal neoplasia are conflicting.

- Whether the elevated CRC risk seen with vitamin D deficient states can be overcome through supplementation is not known. At least one randomized placebo-controlled trial has concluded that vitamin D supplementation for five years did not result in a lower incidence of any invasive cancer, including CRC [265].

  This subject is addressed in detail separately. (See "Vitamin D and extraskeletal health", section on 'Cancer'.)

In addition to these data, there are also some data suggesting an association between poor vitamin D status and mortality in patients with CRC, both in the setting of advanced metastatic disease and resected potentially curable disease. (See "Adjunctive therapy for patients with resected early stage colorectal cancer: Diet, exercise, NSAIDs, and vitamin D", section on 'Vitamin D status' and "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'Issues related to vitamin D'.)

**Magnesium** — Animal studies suggest that dietary magnesium may influence CRC development. A population-based study from Sweden found an inverse association between magnesium intake and the risk of CRC in females [266]. Compared with females in the lowest quintile of magnesium intake, the risk was reduced by approximately 40 percent (RR 0.59, 95% CI 0.40-0.87) in females with the highest quintile of intake. The inverse association was observed for both colon and rectal cancer.

**Garlic** — Consumption of garlic has been associated with a reduced risk of colonic adenomas in some observational studies of patients with CRC and in laboratory studies [267,268]. Garlic has been included as a probable protective factor by the World Cancer Research Fund/American Institute of Cancer Research [227] but a review by the US Food and Drug Administration (FDA) concluded that there was "very limited credible evidence for a relation between garlic consumption and reduced colon cancer risk." Additional prospective intervention studies are needed to settle this issue.

**Fish consumption** — Consumption of omega 3 fatty acids (mainly as fish oil) has been associated with a reduced incidence of colorectal neoplasia in some observational studies, but the data are conflicting:

- A meta-analysis of 22 prospective cohort and 19 case-control studies found an overall lower incidence of CRC among individuals with the highest compared with the lowest fish consumption (summary odds ratio [OR] 0.88, 95% CI 0.80-0.95 ) [269].
- Two grams daily of eicosapentaenoic acid (EPA) as its free fatty acid has been shown in a randomized controlled trial to reduce the numbers of adenomas by a net change of 22.4 percent compared with placebo, as well as to improve the global polyp burden, in familial adenomatous polyposis (FAP) [270].
- On the other hand, in an analysis of data from the placebo-controlled, randomized VITAL (Vitamin D and Omega 3) trial, supplementation with marine omega 3 fatty acids (1 g/day) did not significantly reduce the risk of CRC precursors in the general population [271].

**Coffee intake** — Observational studies have found conflicting evidence on the relationship between coffee consumption and risk of CRC. A link between high rates of coffee consumption and a reduced risk of CRC was reported in a meta-analysis of 12 case-control studies [272] and in three other analyses, one from the National Institutes of Health (NIH)-AARP Diet and Health Study [273], another from the population-based Molecular Epidemiology of Colorectal Cancer (MECC) study [274], and a third from Japan [275]. However, data from the Nurses' Health Study, the Health Professionals Follow-up Study, a meta-analysis of 12 prospective cohort studies, and a pooled analysis of data from 13 prospective cohort studies do not support this finding [276-278].

**Drugs** — Several drugs have been shown to have modest to moderate chemopreventive effects in average- and high-risk populations.

**Aspirin and NSAIDs** — Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may protect against the development of colonic adenomas and is associated with a decreased long-

term risk of colorectal cancer. Further details are discussed separately. (See "NSAIDs (including aspirin): Role in prevention of colorectal cancer" and "Aspirin in the primary prevention of cardiovascular disease and cancer", section on 'Colorectal cancer'.)

**Sulindac plus DFMO or erlotinib** — Chemoprevention with the combination of difluoromethylornithine (DFMO) and sulindac (a nonsteroidal anti-inflammatory drug) has been evaluated in one randomized controlled trial [279]. DFMO is an enzyme-activated irreversible inhibitor of ornithine decarboxylase, the first, and rate-limiting, enzyme in polyamine synthesis. It was initially developed as a chemotherapy agent because of its cytostatic effects on a variety of cell lines.

In the trial, 375 patients with a history of a resected colonic adenoma were randomly assigned to the combination of sulindac plus DFMO or placebo for three years. The trial was halted after an interim analysis found marked significant reductions in the rate of recurrent adenomas (12 versus 41 percent, risk ratio 0.30), advanced adenomas (0.7 versus 8.5 percent, risk ratio 0.09), and multiple adenomas (0.7 versus 13.2 percent, risk ratio 0.06). Active therapy was associated with a higher rate of mild, subclinical adverse changes in the audiogram (18.4 versus 9.8 percent), which improved in some patients after drug discontinuation. Trials evaluating the efficacy and safety of this regimen have been started in FAP and in patients after treatment for early stage CRC.

Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, has also been evaluated in combination with sulindac in patients with FAP. In a randomized placebo-controlled trial, the use of sulindac plus erlotinib for six months resulted in a significantly lower duodenal polyp burden after six months as compared with placebo [280]. However, the utility of this combination is limited by side effects and cost, especially in populations that are not high risk [281]. (See "Familial adenomatous polyposis: Screening and management of patients and families", section on 'Chemoprevention'.)

**Hormone therapy in females** — Postmenopausal hormone therapy (both combined estrogen plus progestin and unopposed estrogen) has been linked to a reduced risk of CRC [282-290], although the data are more consistent for use of combined (plus progesterone) rather than for unopposed estrogen [282,291]. As an example, a reduction in CRC risk was noted in the Women's Health Initiative (WHI) in females taking combined estrogen plus progestin hormone therapy (HR 0.56) [292]. This protective effect remained even after females who reported having screening sigmoidoscopy were excluded. No significant difference in the risk of CRC compared with placebo (HR 1.08) was noted in the unopposed conjugated equine estrogen arm in the WHI [282]. An important finding was that although females receiving combined estrogen and

progestin had a lower diagnosis rate of CRC than did the control group, the tumors that did occur in this group were found at a more advanced stage than those found in the control group.

Longer-term follow-up of the WHI data confirmed that the CRCs diagnosed in females receiving combined hormonal therapy were more advanced at diagnosis (regional or distant metastases in 69 versus 51 percent), and were associated with a nonstatistically significant **higher** mortality rate (37 versus 27 deaths, 0.04 versus 0.03 percent, HR for death 1.29, 95% CI 0.78-2.11) [293]. These data suggest the puzzling possibility that HRT may decrease CRC incidence but not mortality. Such a paradox could be explained by a systematic diagnostic delay in females receiving combined estrogen and progestin postmenopausal hormone therapy or could suggest that HRT actually affects the biology of CRC.

Even prior to the data cited above [293], postmenopausal hormone therapy was not recommended for chemoprevention of colon cancer in females because of the associated long-term risks of therapy. (See "Menopausal hormone therapy: Benefits and risks", section on 'Colorectal cancer'.)

In addition to these data, a protective effect of oral contraceptives in premenopausal females was shown in the Royal College of General Practitioners' Oral Contraception Study [294]. In this study, 46,022 females were recruited in 1968 and 1969 and were observed for up to 44 years. Compared with females who never took them, "ever use" of oral contraceptives was associated with a significantly reduced incidence of CRC (incidence rate ratio 0.81, 95% CI 0.66-0.99).

**Statins** — Some observational data suggest that statins are associated with a protective effect against several cancers, including colon cancer, but overall, the data are conflicting.

The data regarding CRC are as follows:

- A modest reduction in the incidence of colon cancer, as a secondary endpoint, was observed in two large clinical trials evaluating the benefit of pravastatin and simvastatin for coronary artery disease [295,296].

- A reduced risk of CRC was also observed in the MECC study, a population-based case-control study in which data regarding personal and family history of cancer, medical conditions, medication use, physical activity, and nutrition were collected from 1953 patients diagnosed with CRC and 2015 population-based controls matched for age, sex, and ethnicity [297]. In this study, use of statins for at least five years was associated with a significant reduction in the risk of CRC (odds ratio [OR] 0.53, 95% CI 0.38-0.74) after adjustment for use of aspirin and other NSAIDs, physical activity, hypercholesterolemia,

vegetable consumption, and family history. A potential confounding factor is that the cancer population and the controls were drawn from two different databases.

- Other case-control studies have failed to document a protective benefit of statin use against colon cancer [298-301].

The explanation for these conflicting results is unclear.

**Antioxidants** — Several interventional trials have evaluated the efficacy of antioxidants in the prevention of colorectal adenomas. A meta-analysis of eight controlled trials found no convincing evidence that antioxidant supplements had a significant beneficial effect on primary or secondary prevention of colorectal adenomas [302].

**Bisphosphonates** — Oral bisphosphonates are commonly used for the treatment of osteoporosis. (See "Bisphosphonate therapy for the treatment of osteoporosis".)

The possibility that long-term bisphosphonate use was associated with a reduced risk of CRC was initially suggested in two case-control studies and one cohort study [303-305], but not confirmed in a third case-control study [306] or a large prospective cohort study [307].

A meta-analysis of three of these case-control studies with a total of 16,998 CRC cases and 108,197 controls, and one cohort study with 94,405 individuals exposed to bisphosphonates and 283,181 unexposed to bisphosphonates [303-306] suggested a marginally reduced risk of CRC with any exposure to oral bisphosphonates (odds ratio [OR] 0.71, 95% CI 0.78-0.97) [308]. The inverse relationship was statistically significant at a dose of 10 or more prescriptions, or one or more years of oral bisphosphonate use. However, there were two potential problems with this analysis:

- Confounding factors may weaken the conclusions of this study. Obesity (body mass index [BMI] >30 $kg/m^2$) is a risk factor for CRC, and patients with obesity included in the meta-analysis might have been exposed to bisphosphonates less frequently than were patients without obesity. The risk for CRC was adjusted for BMI in only two of the four included studies [309]. (See 'Obesity' above.)

- For unclear reasons, the analysis did not include a second null study of a cohort of 86,277 females enrolled onto the Nurses' Health Study, 801 of whom developed CRC [307]. The age-adjusted HR for CRC among females who regularly used bisphosphonates was 0.92 (95% CI 0.73-1.14) and was further attenuated after adjustment for other risk factors (HR 1.04, 95% CI 0.82-1.33). Risk was not influenced by duration of therapy.

On the other hand, a later meta-analysis that did include the Nurses' Health Study data also concluded that the use of bisphosphonate was associated with a modestly reduced risk of CRC (pooled RR 0.89, 95% CI 0.81-0.98) [310].

**Angiotensin II inhibition** — In vitro and in vivo data suggest that angiotensin II is involved in promoting cancer development and that there is a relationship between angiotensin II inhibition and reduced colon cancer cell growth. However, several observational studies and secondary analyses of data from clinical trials examining the relationship between antihypertensive therapy with an angiotensin II-converting enzyme inhibitor (ACE-I) and CRC risk have yielded conflicting results [311-314]:

- A cohort study reported that long-term use of lisinopril was associated with a 41 percent reduction in the risk of advanced colorectal adenoma [311].
- Another case-control study assessing ACE-I exposure among 665 patients with CRC failed to demonstrate a significant association; however, the sample size was small and the duration of exposure was short [312].
- A secondary analysis of data from randomized trials also did not find an association between use of an ACE-I or angiotensin receptor blocker (ARB) and CRC risk, although the follow-up durations in the included trials were relatively short [313].
- By contrast, a large nested case-control study among a cohort of patients with hypertension in the EPIC General Practice Research Database provides modest evidence of a potential protective effect of angiotensin II inhibition on CRC risk [314]. Overall, 2847 case patients (diagnosed with CRC after the diagnosis of hypertension) were matched (for age, sex, calendar year, and duration of follow-up) with 28,239 controls, and the average duration of follow-up in both groups was 4.4 years. The adjusted odds ratio (OR) for CRC was 0.84 (95% CI 0.72-0.98) for three or more years of ACE-I/ARB therapy and 0.75 (95% CI 0.58-0.97) for five or more years of exposure. The strength of the association increased with higher dose therapy (OR 0.53, 95% CI 0.35-0.79 for three or more years of high-dose exposure). CRC rates were significantly lower among patients exposed to ACE-I/ARB therapy alone when compared with those exposed to other antihypertensive agents exclusive of angiotensin inhibition.

Taken together, these observational data suggest a potential protective effect of angiotensin II inhibition on CRC risk that is more evident in those receiving long-term and high daily dose therapies, but no intervention trials have thus far shown such an effect.

## 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.)

- Beyond the Basics topics (see "Patient education: Screening for colorectal cancer (Beyond the Basics)")

## SUMMARY

- **Risk factors and influence on screening recommendations**
  - The major factors that increase the risk of colorectal cancer (CRC) and influence screening recommendations are certain hereditary forms of CRC, age, a personal or family history of sporadic CRC (and possibly large or advanced adenomas), inflammatory bowel disease, and a history of abdominal irradiation. (See 'Factors that currently influence screening recommendations' above.)
  - Several potentially modifiable factors, including obesity, diabetes, tobacco use, excess consumption of alcohol, excess consumption of processed meat, and lack of physical activity, have been consistently identified as risk factors in observational studies, but at present, they do not alter screening recommendations. Patients may be counseled about these associations and encouraged to reduce or avoid such factors for the primary prevention of CRC. (See 'Risk factors that do not alter screening recommendations' above.)
  - Other risk factors have been identified, including race, sex, acromegaly, and a history of renal transplantation, but their influence on screening recommendations has been

variable. (See 'Factors that may influence screening recommendations' above.)

- **Protective factors**

  - A substantial body of evidence supports a protective effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) on the development of colonic adenomas and cancer. The potential role of aspirin and other NSAIDs in CRC prevention is discussed separately. (See "Aspirin in the primary prevention of cardiovascular disease and cancer" and "NSAIDs (including aspirin): Role in prevention of colorectal cancer".)

  - Other protective factors have also been identified, mainly in observational studies, but the strength of some of these associations is uncertain. (See 'Protective factors' above.)

  - Specific types of diets may reduce the risk of CRC. Despite the uncertainty, a protective diet can be defined for clinical purposes to include avoidance of processed and charred red meat, inclusion of vegetables (especially cruciferous) and unprocessed forms of wheat bran (controversial), an adequate amount of folate intake from food, limited caloric intake, and avoidance of excessive alcohol.

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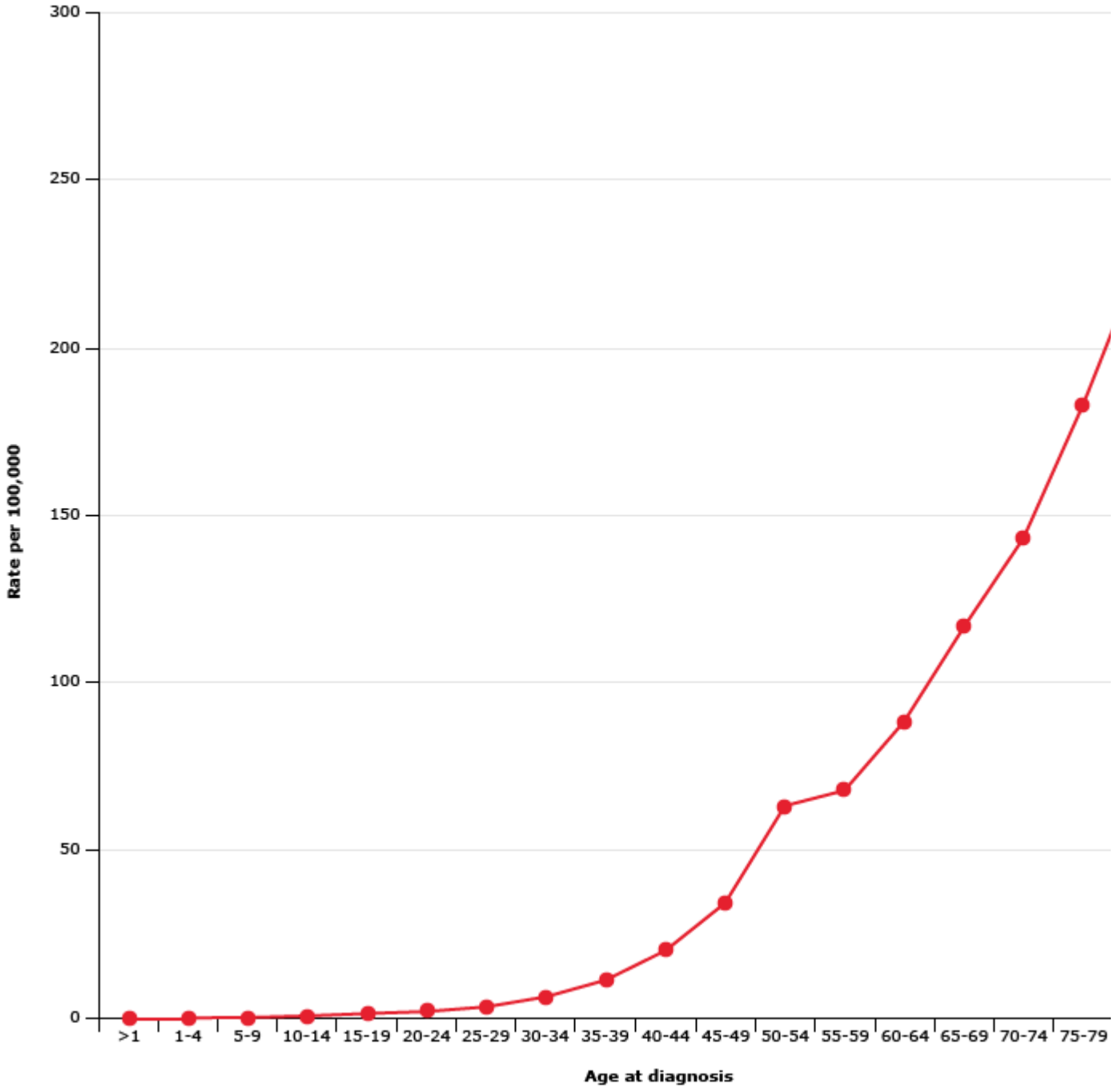
Topic 2606 Version 121.0

## GRAPHICS

### Increasing incidence of colorectal cancer in the United States with age, SEER 20




The age-specific incidence of colorectal cancer was measured between 2014 and 2018 in men and women o

SEER: Surveillance, Epidemiology, and End Results.

*Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2014-2018. Available at: https://seer.cancer.gov/explorer/app site=20&data_type=1&graph_type=3&compareBy=sex&chk_sex_1=1&rate_type=2&race=1&advopt_precision=1&advopt_show_ci=on&c*

=2 *(Accessed on July 13, 2021).*

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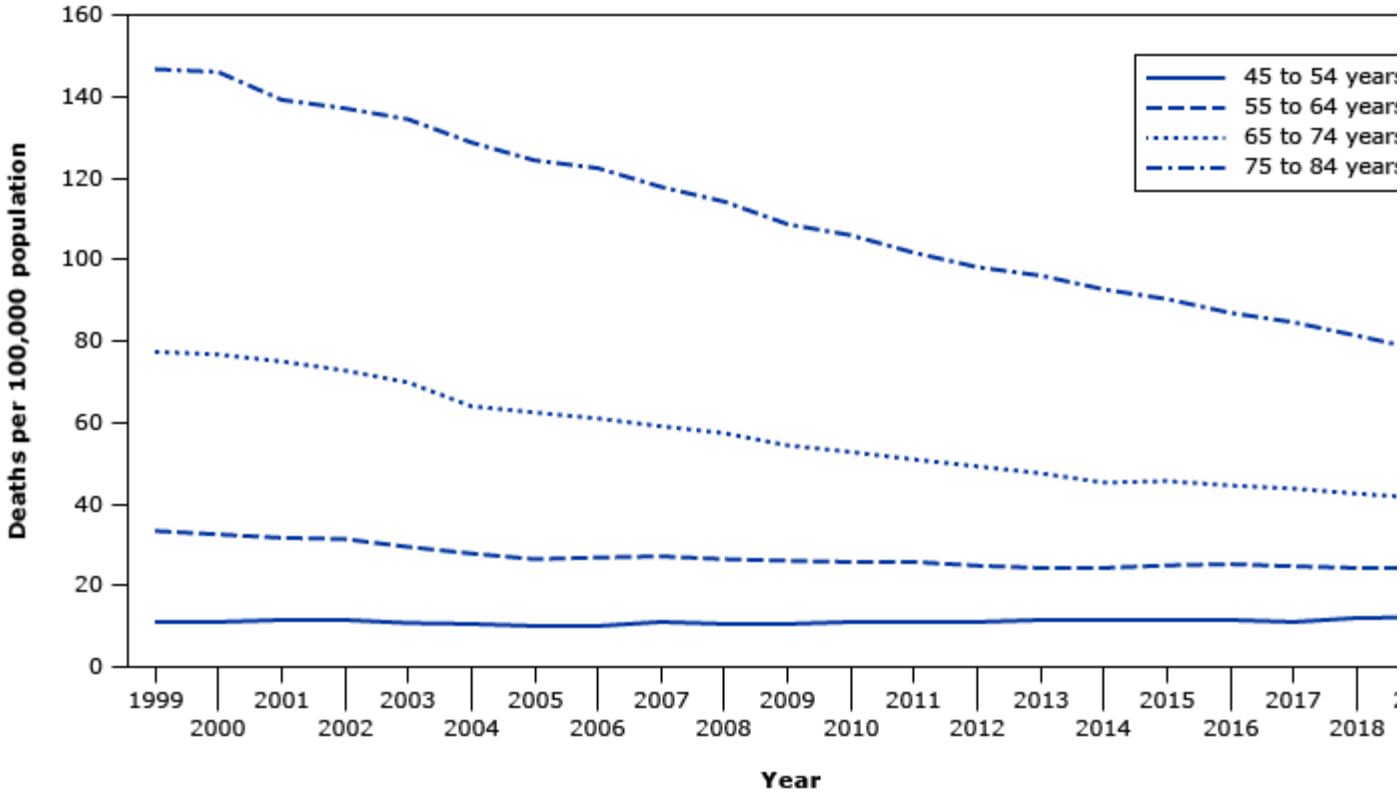
Graphic 111996 Version 3.0

## Death rates* from colorectal cancer,¶ by age group, in the United States 1999 t




During 1999 to 2019, deaths per 100,000 persons from colorectal cancer decreased among persons aged 55 64 years (from 33.5 to 24.4), persons aged 65 to 74 years (from 77.4 to 41.5), and persons aged 75 to 84 year (from 146.7 to 77.9). The death rate from colorectal cancer among persons aged 45 to 54 years generally increased from 1999 (11.1) to 2019 (12.0). In each year during 1999 to 2019, the death rate was highest amo persons aged 75 to 84 years and lowest among persons aged 45 to 54 years.

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* Deaths per 100,000 population in each age group.

¶ Deaths from colorectal cancer were identified using International Classification of Diseases, Tenth Revisior underlying cause-of-death codes C18-21.

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*Reproduced from: QuickStats: Death Rates from Colorectal Cancer, by Age Group — United States, 1999–2019. MMWR Morb Mortal W Rep 2021;70:1233.*

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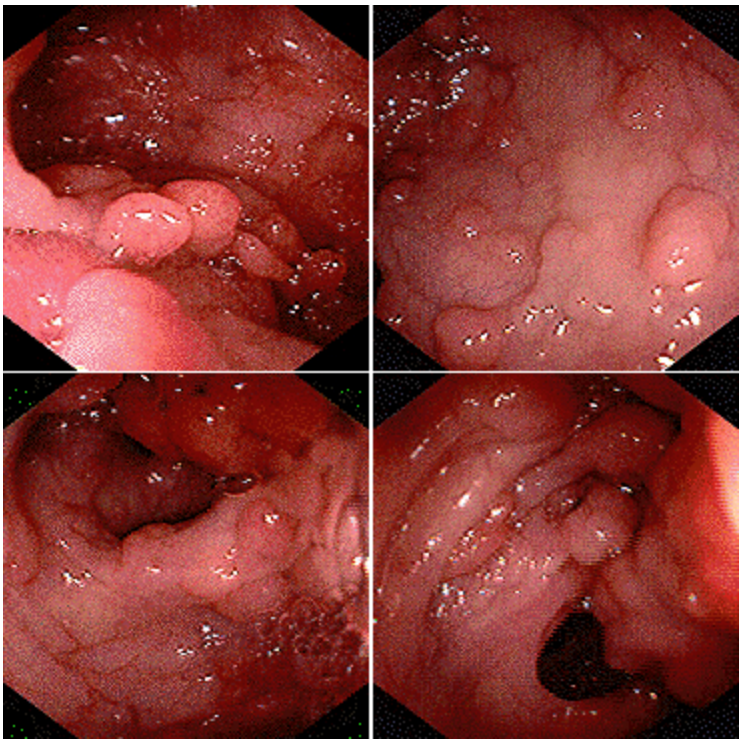
Graphic 132611 Version 1.0

## 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.

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*Courtesy of James B McGee, MD.*

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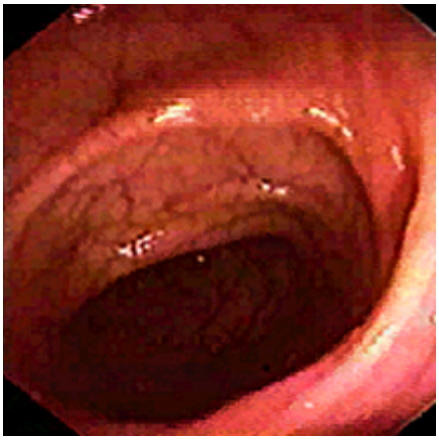
Graphic 59413 Version 2.0

## 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.

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*Courtesy of James B McGee, MD.*

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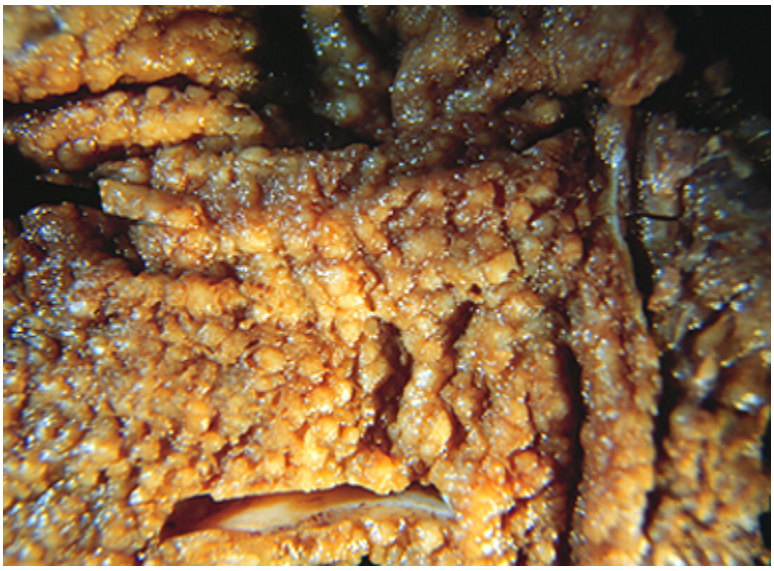
Graphic 55563 Version 1.0

## Multiple colorectal polyps in patients with familial adenomatous polyposis



Gross specimen of the colon from a patient with familial adenomatous polyposis shows innumerable small polyps.

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*Courtesy of Robert Odze, MD.*

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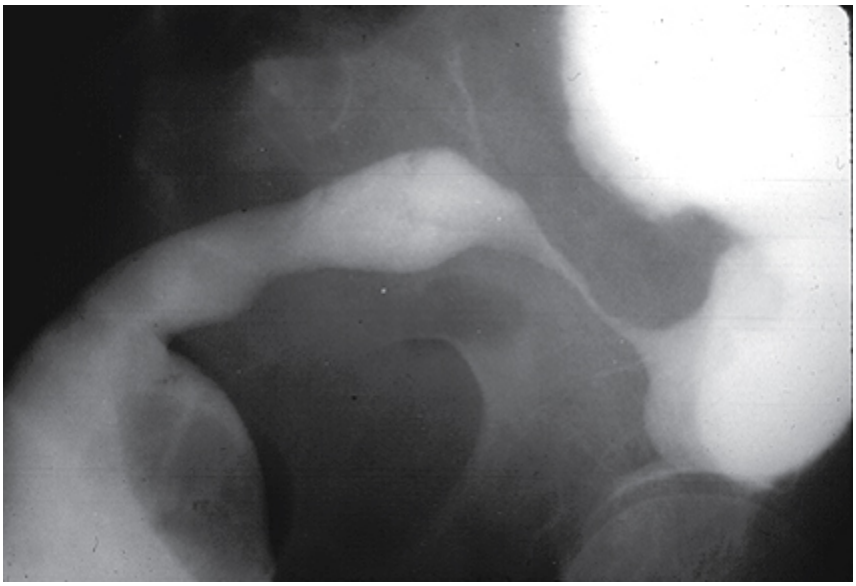
Graphic 73267 Version 3.0

## Sigmoid cancer developing in ulcerative colitis, as seen on barium enema



Barium enema study demonstrates a focal stricture in the sigmoid colon caused by an infiltrating cancer. The adjacent bowel is featureless and folds are absent, findings characteristic of chronic ulcerative colitis.

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*Courtesy of Norman Joffe, MD.*

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Graphic 63411 Version 3.0

## Contributor Disclosures

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Conflict of interest policy

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