Risk Factors for Colorectal Polyps and Cancer

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KEYWORDS

• Risk factors • Polyps • Adenomas • Colorectal cancer • Serrated polyps
• Epidemiology

KEY POINTS

- The primary nonmodifiable risk factors for colorectal adenomas are age, sex, and family history.
- Modifiable risk factors consist of alcohol, obesity, physical activity, and diet.
- Obscure risk factors for colorectal adenomas include acromegaly, hereditary hemochromatosis, and patients who have had ureterosigmoidostomy.
- Serrated class polyps have different risk factors than conventional adenomas.

INTRODUCTION

Colorectal cancer (CRC) is among the most highly incident and deadly cancers in the United States and worldwide, resulting in nearly 1 million deaths per year across the globe.[1–6] Most CRCs arise from precursor adenomatous or serrated polyps, presenting the opportunity for CRC prevention via the detection and removal of precancerous lesions before they progress to malignancy and metastasis. A rich literature on the epidemiology of CRC and colorectal polyps has been published in the past 30 years that demonstrates that risk factors for sporadic CRC and its precursor polyps are largely similar. There are important differences in risk factors for adenomatous and serrated class polyps, however. Herein, the authors review this literature, with particular focus on nonmodifiable, modifiable, and certain unusual or overlooked factors that are of importance to gastroenterologists, patients, and public health professionals.

Colorectal polyps are defined as aberrant growths that typically arise from the mucosal layer of the large intestine and extend into the lumen. Colon polyps are

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subdivided into neoplastic and nonneoplastic lesions. The predominant nonneoplastic polyps are inflammatory polyps, hamartomas, lymphoid polyps, mucosal prolapse polyps, and hyperplastic polyps. Neoplastic polyps, meanwhile, are characterized based on their potential to undergo malignant transformation and include primarily adenomatous and serrated polyps. Adenomatous polyps, the primary focus of this review, compose two-thirds of all colon polyps and are the most common precursor lesions to CRC. Histologically, conventional adenomas are categorized into tubular, tubulovillous or villous histologic subtypes. Neoplastic serrated polyps include traditional serrated adenomas and sessile serrated lesions (SSLs, also known as sessile serrated adenomas or polyps). SSLs are the most common premalignant serrated polyp type, and are predominately located in the right colon. As described in other chapters, conventional adenomas and serrated polyps exhibit different mutogenic pathways to invasive CRC.

NONMODIFIABLE RISK FACTORS

Nonmodifiable risk factors for adenomatous polyps include age, sex, race/ethnicity, genetic polyposis syndromes, and family history. Although these characteristics are generally immutable, identification of high-risk individuals can lead to improved screening and surveillance of precancerous lesions.

Age

Age is the predominant nonmodifiable risk factor in the development of colon adenomas. A large body of research has shown that the prevalence of adenomas increases predictably with age, rising 10% to 15% from individuals aged 50 to 55 years to the oldest age stratum at 70 to 75 years.[7,8] This effect of age on colon polyp risk holds true despite stratification by sex and ethnicity. Serial epidemiologic necropsies conducted in patients 20 to 89 years corroborate the increasing prevalence of polyps with age, noting a risk inflection point at age 50 years.[9] Recent data from a large US endoscopy quality improvement database clearly demonstrate this pattern (**Fig. 1**).[7] Likewise, age increases one's risk of large polyps, and the Clinical Outcome Research Initiative (CORI) revealed that patients older than 69 years have an odds ratio (OR) of 2.7 for polyps greater than 9 mm compared with patients younger than 50 years.[10,11]

Because of longstanding guidelines that (until recently) recommended initiating CRC screening at age 50 years, there is a paucity of colon polyp epidemiologic data on patients less than 50 years; however, the concerning increase in incidence of CRC in younger patients prompts investigation into colon polyps within these younger cohorts. A study by Dave and colleagues[12] comprising data from patients 20 to 49 years of age undergoing colonoscopy between 2016 and 2019 found that 20% of patients had neoplastic polyps, with 24% of patients in the 30- to 40-years age group and 37% in the 40- to 49-years age group. An increasing incidence of advanced polyps in younger patients correlates with the higher rates of CRC in patients under 50 years.[13–15] These data support the recent recommendation of the US Preventive Services Task Force to lower the age of initiation of CRC screening from 50 to 45 years.[16] Nevertheless, colorectal polyps and CRC are much more common in older individuals than they are in patients less than 50 years.

Sex

The prevalence of colon adenomas is consistently higher in men than women; however, despite this risk discrepancy, lifetime incidence is approximately equal between

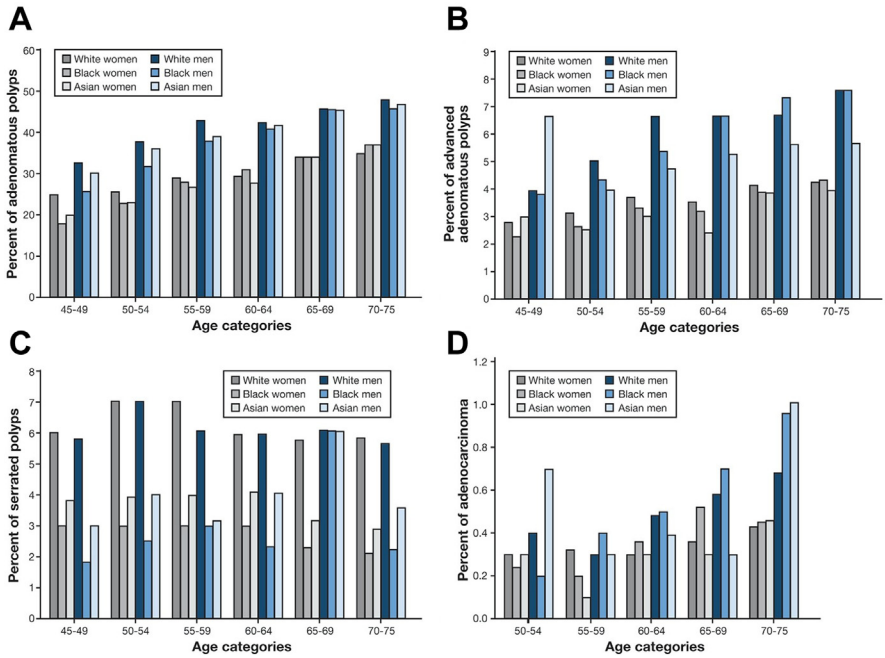

Fig. 1. Polyp and CRC data from a large sample of average risk screening colonoscopies in the United States from the GI Quality Improvement Consortium (GIQuIC), showing prevalence of adenomatous polyps (*A*), advanced adenomas (*B*), serrated polyps (*C*), and colorectal adenocarcinoma (*D*), stratified by age, sex, and race. Graphs demonstrate that (1) men are at higher risk of adenomatous polyps and CRC compared with women; (2) prevalence increases by age for adenomas, advanced adenomas, and CRC, but not for serrated polyps; and (3) white race is associated with a higher risk of serrated polyps than other races. (*From* Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, Shaheen NJ, Barritt AS, Lieber SR, Kochar B, Barnes EL, Fan YC, Pate V, Galanko J, Baron TH, Sandler RS. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2019 Jan;156(1):254-272.e11.)

the sexes, as women tend to live longer. One cross-sectional study reported that men have 1.77 times the risk of adenomas on screening colonoscopy compared with women.[8] The CORI database revealed that men also had a 50% increased risk of large polyps (>9 mm) compared with women (OR, 1.5; 95% confidence interval [CI], 1.42–164).[17] Men also appear to have increased risk of polyps on surveillance colonoscopy compared with women.[11] The higher prevalence of colon polyps in men versus women is reflected in the Gastroenterology Society guidelines for adenoma detection rate targets, of 25% for women and 30% for men.[18] It is important to note that this sex discrepancy in adenoma prevalence is not true of sessile serrated polyps, which are equally prevalent among men and women (see **Fig. 1**).[19] The reduced risk of adenomatous polyps in women has been hypothesized to be related to estrogen receptor genes, decreased insulin-like growth factors, and/or reduced bile acid production.[17,20–22]

Race and Ethnicity

Epidemiologic studies demonstrate that there are minor differences in risk of adenomas based on race and ethnicity.[8] In particular, proximal adenoma risk is around

25% higher in blacks than whites, and this risk is reflected in proximal colon cancer rates as well.[23,24] African Americans also have a higher risk of large polyps (>9 mm) on screening colonoscopy until age 65 years at which point the prevalence between blacks and whites is equivalent. However, it is well known that African Americans have a higher incidence and mortality of CRC compared with other racial groups. A Department of Veterans Affairs cohort of 4038 veterans revealed that 24% of African American patients on screening colonoscopy had villous pathologic condition compared with only 16% of Caucasians.[25] This indicates that despite equitable health care access, African Americans could have higher rates of more aggressive polyp histology. Particularly concerning, the incidence and mortality of CRC in Alaskan Natives are double that of the African American population.[26] Meanwhile, Hispanic persons have a 25% lower risk of large adenomas than non-Hispanic whites from 50 to 79 years,[27,28] and Asian Americans appear to have an adenoma prevalence similar to whites.[8]

Racial and ethnic differences are difficult to study because of heterogeneity within groups and the inability to disentangle lifestyle factors from genetics. For example, although native Japanese populations have a low prevalence of adenomatous polyps, Hawaiian ethnic Japanese have a higher adenoma prevalence at around 61%.[29] This is further illustrated by differing risk of large polyps observed in Hispanic persons from Mexican-predominant states and non-Mexican-predominant states.[30] Overall, there appears to be subtle differences between ethnic groups in polyp risk that may largely be driven by lifestyle exposures or other factors.

High-Risk Genetic Syndromes

There are several well-described hereditary polyposis syndromes, including familial adenomatous polyposis, serrated polyposis syndrome, MYH-associated polyposis, polymerase proofreading associated polyposis, juvenile polyposis syndrome, and Peutz-Jeghers syndrome.[31] Hereditary nonpolyposis CRC syndrome, or Lynch syndrome, is associated with an increased risk of malignancy that can occur with or without precursor polyps.[32] Further discussion of these genetic syndromes is beyond the scope of this review, which focuses primarily on sporadic colorectal polyps, but is outlined clearly within recent guidelines.[33]

Family History of Colorectal Cancer

Having a first-degree relative with a history of CRC increases one's risk of colon cancer substantially. In fact, the risk of CRC increases by a factor of 1.76 (CI, 1.59–1.94) in patients who have a first-degree family member diagnosed with CRC, even after age 80 years.[34] Patients who have a first-degree relative with CRC also have an increased risk of adenomas in general (OR, 1.82; 95% CI, 1.66–2.00) as well as a higher risk of advanced adenomas (OR, 2.43; 95% CI, 1.66–2.00).[35,36] This body of research has prompted the US Multi-Society Task Force on Colorectal Cancer to recommend that patients with a first-degree family member with CRC or advanced polyp start screening colonoscopy at age 40 or 10 years before the age of youngest affected relative, and that patients with a first-degree relative with CRC under the age of 60 years undergo closest surveillance.[37,38]

Family History of Polyps

A recent Swedish case-control study reported that patients with a first-degree relative with a colorectal polyp had a 40% higher risk of polyps themselves.[39] Interestingly, the investigators reported that the risk of colorectal polyps increases with each additional first-degree relative with polyps as well as a decreasing age at diagnosis of polyps in

family members. Similarly, Ahsan and colleagues[40] found that having a family member diagnosed with polyps at age less than 50 years increases one's own risk of polyps by 4 times compared with having a family member diagnosed with polyps after age 60 years. However, despite the findings above, given that roughly half of average risk persons undergoing screening colonoscopy harbor at least 1 adenomatous polyp, having a first-degree relative with small or diminutive polyps is unlikely to be associated with an appreciably elevated risk of CRC. In addition, the difficulty of ascertaining an accurate family history of polyps limits the clinical applicability of these findings.

Personal History of Polyps or Colorectal Cancer

Both the number and the size of adenomatous polyps on one's baseline examination increase the risk of developing both future advanced adenomas and CRC. Martínez and colleagues,[41] in a pooled prospective analysis, found that having greater than 5 adenomas at baseline colonoscopy or having at least 1 adenoma greater than 19 mm in size increased absolute risk of metachronous advanced adenoma by approximately 20% to 25%. In addition, patients with a history of CRC also have a risk of metachronous CRC that is at least 70% higher than the expected population rate.[42]

Inflammatory Bowel Disease

Patients with IBD with colonic involvement (ulcerative colitis [UC] and Crohn colitis involving at least 30% of the colon) are at a higher risk of CRC than the general population.[43] For this reason, colonoscopy surveillance is recommended starting 8 to 10 years after the onset of colitis symptoms.[44,45] Compared with expected population incidence, patients with UC with proctitis have an OR of 1.7 for CRC, patients with left-sided colitis have an OR of 2.8, and patients with pancolitis have an OR of 14.8.[46] However, most CRC in IBD bypasses the traditional sporadic adenoma-to-carcinoma sequence and is instead defined by nonpolypoid dysplasia with late APC mutations.[47] Patients with primary sclerosing cholangitis with UC have an exceedingly high risk of CRC, with an OR of 4.79 for developing CRC compared with patients with UC without primary sclerosing cholangitis.[48,49]

Despite the higher risk of CRC in UC, patients with UC are at roughly equivalent risk of colon adenomas compared with the general population.[47,50] A prospective surveillance study by Rutter and colleagues[51] found that CRC incidence in UC has dropped substantially from 1970 to 2000, likely attributable to newer IBD therapies and increased use of surveillance colonoscopy. It has also been hypothesized that mesalamine has a chemoprotective effect, and it has been shown to induce apoptosis and curb mucosal proliferation in patients with sporadic polyps.[52] Interestingly, patients with IBD that do have adenomas have a greater risk of developing advanced neoplasia than patients with matched adenoma without IBD.[53]

Diabetes

Diabetes has been noted to increase the risk of colorectal adenomas within younger age groups. Patients with diabetes aged 40 to 49 years have a 3 times greater risk of polyps than nondiabetic patients within the same age group. In fact, patients with diabetes aged 40 to 49 years had just as many polyps as nondiabetic patients in the 50- to 59-years age group.[54] Among all age groups, diabetes increases polyp risk by 50%. Although hyperglycemia is associated with CRC risk, it is unclear if hyperglycemia or hyperinsulinemia specifically is the dominant driver of polyp risk.[55,56]

MODIFIABLE RISK FACTORS

Although there are several nonmodifiable risk factors for precancerous polyps and CRC, such as age, sex, and family history,[57,58] as discussed above, several modifiable risk factors and protective factors have also been identified (**Table 1**). Identification and management of these risk factors are important in assessing and potentially decreasing patients' risk for CRC. Indeed, it is hypothesized that upwards of two-thirds of CRC cases are attributable to modifiable risk factors.[59] Given the relatively long latency period from adenoma to invasive cancer,[60,61] modification of such risk factors has the potential to mitigate CRC risk in some patients.

Smoking

Tobacco smoking is an important risk factor for the development of CRC and colonic polyps.[57] The mechanism for this association is via oxidative stress and damage to cellular DNA.[62] Specifically, carcinogens in smoke diffuse passively through the circulatory system into the colonic mucosa, interrupting cellular replication and hindering the DNA repair process.[62] In addition, the carbon monoxide in cigarette smoke indirectly leads to DNA mutations and cellular hypoxia.[62] In fact, compared with nonsmokers, both current (OR, 1.29; 95% CI, 1.11–1.49) and former smokers (OR, 1.18; 95% CI, 1.05–1.32) have an increased risk of adenomatous polyps.[63] Smoking also increases the risk of serrated polyps. In a meta-analysis examining this association, there was an increased risk of the development of SSLs in smokers in comparison to nonsmokers (relative risk [RR], 2.47; 95% CI, 2.12–2.87).[59,64] Some studies suggest that smoking increases the risk of serrated polyps primarily within the distal colon.[65] Smoking also increases the risk of CRC in a dose-dependent manner.[66] Recent studies have shown that the risk of CRC decreases after 25 years of smoking cessation, underpinning the importance of counseling for smoking cessation.[67]

Alcohol Use

Alcohol use is common with a prevalence of 60% of adults in the United States.[68] Numerous studies confirm that consuming greater than 1 alcoholic beverage per day has been shown to have a clear relationship with the development of both colon polyps and CRC.[69] One Korean study found that significant alcohol consumption increased the risk of adenomas on surveillance colonoscopy by approximately 86% compared with nondrinkers.[70] Another study, by Bardou and colleagues,[71] similarly demonstrated an increased risk of large adenomas (>10 mm) in heavy drinkers (OR, 1.8; 95% CI, 1.2–2.7) compared with control patients. With respect to serrated polyps, a 2015 meta-analysis demonstrated a 24% increase in risk of serrated polyps in subjects who drank alcohol daily compared with nondrinkers. More specifically, there was a dose-dependent relationship with alcohol and serrated polyp risk, with an RR of 1.19 (95% CI, 1.02–1.40) for moderate drinkers (8–36 g/d) and 1.60 (95% CI, 1.35–1.91) for heavy drinkers (>36 g) compared with nondrinkers.[72] A recent analysis using pooled data from the Nurses' Health Study and the Health Professions Follow-up Study (n = 141,143) found that heavy alcohol drinkers had a higher risk of both conventional adenomas (OR, 1.17; 95% CI, 1.10–1.25) and serrated polyps (OR, 1.33; 95% CI, 1.24–1.43) compared with never drinkers.[64,73]

Obesity

Obesity accounts for nearly 3 million deaths per year.[74] One explanation for excess mortality in this group is an increased risk of malignancy, including CRC.[57] It is hypothesized that those who are obese have higher levels of chronic inflammation because of

Table 1
Risk factors associated with adenomatous polyps, serrated polyps, and colorectal cancer

Risk Factor	Adenomatous Polyps	Serrated Polyps	Colorectal Cancer
Nonmodifiable			
Older age	Increased risk	Minimal or no increased risk	Increased risk
Male sex	Increased risk	No increased risk	Increased risk
Family history of CRC	Increased risk	Minimal or no increased risk	Increased risk
Modifiable			
Smoking	Increased risk	Increased risk	Increased risk
Alcohol	Increased risk	Increased risk	Increased risk
Red meat	Increased risk	Increased risk	Increased risk
Calcium/vitamin D/folate	Decreased risk	Increased risk	Decreased risk
NSAIDs/aspirin	Decreased risk	Decreased risk	Decreased risk
Rare			
Acromegaly	Increased risk	Unknown	Increased risk
Hereditary hemochromatosis	Unknown	Unknown	Increased risk
Ureterosigmoidostomy	Increased risk	Unknown	Increased risk

the release of proinflammatory cytokines (tumor necrosis factor, interleukin-6) from adipose tissue.[62,75] One meta-analysis found that a 5-unit increase in body mass index (BMI) was associated with a 19% higher risk of a colorectal adenomas.[75] This was supported in another study that noted a 2% to 3% increase in CRC risk with each increase in BMI unit.[57] Patients with high waist circumference also appear to have an increased risk of metachronous neoplasia.[76]

Physical Activity and Exercise

Physical activity decreases the risk of both CRC and adenomas. A meta-analysis found a 16% decrease in risk of adenomas in the most active men and women compared with sedentary participants.[77] In men, the most physically active quartile had a significantly lower risk of adenomatous polyp recurrence and those in the least physically active quartile.[78]

Diet

Red meat has been implicated with an increased risk of CRC as well as colorectal adenomas.[57,62] One study found this risk of adenoma recurrence was increased (OR, 1.85; 95% CI, 1.10–3.13) in those who consumed cooked red meat when compared with those who did not.[79] The pathogenesis is thought to be related to the production of heterocyclic amines, which have a direct effect on the DNA production/mutation process.[62] One study found that for every 100 g of red meat consumed daily, there was a 1.16 times (95% CI, 1.04–1.30) elevated risk of CRC.[57,80] Indeed, the American Cancer Society guidelines recommend limiting red meat in order to mitigate the risks of CRC.[64]

In contrast, there is evidence to suggest that the consumption of a Mediterranean diet (defined as low in saturated fats, meat, and dairy, and high in vegetables, fruits, and nuts[81]) or vegetarian diet decreases risk of CRC (OR, 0.86; 95% CI, 0.80–0.92).[69] The additive effects of a healthy balanced diet, including higher quantities of whole grains, dairy, fruits, and vegetables, and lower content of saturated fat content (specifically red meat), are thought to be responsible for the reduced risk of CRC.[69]

Several epidemiologic studies have found that both dietary calcium intake and vitamin D intake are associated with decreased risk of CRC.[82,83] The mechanisms of both are hypothesized to regulate cell proliferation and apoptosis.[84] Milk intake has a similar level of evidence, as it contains both calcium and vitamin D.

Fiber has convincing evidence to support a lower risk of CRC (RR, 0.84; 95% CI, 0.78–0.89) and recurrence rate of colorectal polyps.[39,84,85] The mechanism by which fiber mitigates CRC risk is uncertain, but may be due to its effects on stool transmit time, diluting carcinogenic colonic contents, and forming fatty acids that can regulate apoptosis.[62,80,84] Specifically, whole grain intake is also associated with decreased CRC risk (RR, 0.88; 95% CI, 0.83–0.94).[80,86]

Fruits are thought to have anticarcinogenic properties, and there is limited evidence that high fruit intake is associated with a decreased risk of CRC.[80,84,86] There is no clear evidence that vitamin B6, A, C, and E, methionine, coffee, and caffeine affect CRC risk.[80] A healthy and balanced diet may also influence the gut microbiome in a beneficial manner, and in doing so, decrease the production of certain bacterial metabolites that can be carcinogenic.[87]

Medications

Many different compounds have been studied for their chemopreventive properties with respect to CRC over the past 40 years. A detailed discussion of these agents is beyond the scope of this review but can be found elsewhere.[88,89] Suffice to say that several medications have been found to affect the risk of CRC, most notably aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone replacement therapy. In a study published in 2020 from data collected from 1980 to 2014 involving more than 94,000 participants, those who used aspirin on a daily basis had a decreased risk of CRC compared with those who did not (hazard ratio [HR], 0.80;

95% CI, 0.72–0.90).[90] Importantly, this risk was only applicable to those 70 years old or older who had initiated aspirin use before the age of 70. There was no benefit to initiating aspirin after the age of 70.[90] Furthermore, it was found in multiple studies that this protective effect may be stronger in the proximal colon.[59,60] Accordingly, a recent Clinical Practice Update from the American Gastroenterological Association recommended use of aspirin for prevention of CRC in certain persons based on their age and cardiovascular risk profile.[89]

In patients with diabetes, metformin use is associated with a decreased risk of CRC (OR, 0.73; 95% CI, 0.62–0.86) compared with diabetics not taking metformin.[91] Hormone replacement therapy for postmenopausal women has also been studied and shown to mitigate the risk of CRC. Specifically, those who take estrogen on a daily basis were found to have up to a 40% decreased risk of CRC compared with women who did not.[92] The estrogen receptor gene hypothesis is supported by findings from the Nurses' Heath Study, which demonstrated that postmenopausal women on hormone replacement therapy had a decreased risk for large adenomas.[93,94]

Despite the reduced risk of CRC observed with aspirin, NSAIDs, and hormone replacement therapies, the inherent risks of these medications, including bleeding, heart disease, and other malignancies, limit their broad application in chemoprevention.

RARE OR UNUSUAL RISK FACTORS FOR COLORECTAL CANCER

Additional rare factors have been linked to developing CRC, such as acromegaly, hereditary hemochromatosis, ureterosigmoidostomy, and history of childhood cancer.

Acromegaly

Acromegaly poses increased risk of CRC because of excess growth hormone and insulin-like growth factor 1, which cause colonic epithelial cell proliferation, diminished cellular apoptosis, slowed intestinal transit, and redundant bowel.[95]

A study by Rokkas and colleagues[96] involving 701 patients with acromegaly demonstrated increased risk of both adenomatous polyps (OR, 2.54; 95% CI, 1.91–3.26), and CRC (OR, 4.35; 95% CI, 1.53–12.35).[95] A more recent meta-analysis involving 529 patients with acromegaly found a standard incidence ratio (SIR) of 2.6 (95% CI, 1.7–4.0) for CRC.[95,97] Similarly, another study (n = 700) found that patients with acromegaly have a 2.4-fold increased risk of colonic adenomas and a 7.4-fold greater risk of CRC.[95] However, a separate meta-analysis in 2017 (n = 3896) revealed contradictory findings from multiple retrospective analyses, suggesting that the data regarding CRC risk in acromegaly are insufficient.[98,99] Furthermore, the impact on mortality remains unclear.[95]

Hereditary Hemochromatosis

HH is an inherited genetic disorder of iron overload with increased iron absorption and possible risk for CRC. Iron can be carcinogenic via forming hydroxyl free radicals, dampening immune response, and being a nutrient for carcinogenesis.[100] Both HFE gene mutations are common and estimated to be approximately 15% of the US population.[101] A Melbourne cohort study (n = 28,509) found that C282Y homozygotes were at a 2-fold increased risk of CRC (HR, 2.28; 95% CI, 1.22–4.25).[100] However, heterozygotes were not at an increased risk in this study.[100] Shaheen and colleagues[101] in a case-control study (n = 1308) found that subjects with any HFE gene mutation were significantly more likely to have CRC than subjects with no HFE gene mutations (OR, 1.40; 95% CI, 1.07–1.87). Other studies that support an association between HH

and CRC include a Swedish cohort study (n = 6849) that reported that patients with HH had a 40% increased for colon adenocarcinoma (SIR, 1.4; 95% CI, 1.1–1.9), and Nelson and colleagues (n = 1950),[102,103] which showed a small increased risk for CRC among patients heterozygous for HH (RR, 1.28; CI, 1.07–1.53). Some studies found an association with CRC in only male *HFE* C282Y homozygotes, and one study found no association.[104,105] Overall, the evidence is compelling that special attention to risk for CRC be attributed to patients with the HFE gene and HH especially in homozygotes.

Childhood Cancer Survivors

Childhood cancer survivors are at risk for gastrointestinal subsequent malignant neoplasms. The British Childhood Cancer Survivor Study (n = 17,981) demonstrated an SIR of 4.6 for digestive malignancies, with the greatest SIR observed following Wilm's tumor and heritable retinoblastoma.[106] Henderson et al. showed at 22.8-year median follow up (n=14,358) an increased risk of subsequent gastrointestinal cancer that was 4.6-fold higher than the general population.[107] Abdominopelvic radiation posed the highest risk (SIR = 11.2; 95% CI 7.6-16.4), followed by previous receipt of procarbazine or platinum drugs.[107] Nottage et al. found that among childhood cancer survivors (n = 13,048), the 40-year cumulative incidence of secondary CRC was 1.4%, with a SIR of 10.9 (95% CI, 6.6 to 17.0) compared to the general population.[108] The same authors also reported that abdominopelvic radiation (dose-dependent) and alkylating agents increased the risk.

These findings were further corroborated by Daniel et al., who demonstrated that children exposed to abdominopelvic radiotherapy had a 4- to 11-fold greater risk of CRC.[109]

Despite these findings, the appropriate screening strategy remains unclear.[110] The Children's Oncology Group recommends colonoscopy every 5 years or stool testing every 3 years following abdominopelvic radiation beginning either at age 30 or 5 years after radiation exposure.[111]

Ureterosigmoidostomy

Ureterosigmoidostomy is a procedure where the ureters are inserted into the sigmoid colon, typically following cystectomy for bladder cancer. Ureterosigmoidostomy increases the risk of CRC with an incidence of 2-15%.[112] The mean latency times from surgery to adenoma and CRC are estimated to be 20 years and 26 years respectively.[112,113] Carcinogenesis is proposed to involve colonic exposure to urinary amines and amides that undergo N-nitrosation with colonic bacteria.[114] Ureterosigmoidostomy is a less favored operation in the current era because of multiple complications, including malignancy, and thus is now rarely performed, having been replaced by newer techniques of urinary diversion procedures. However, clinicians should be aware that patients who did have this surgery performed should undergo yearly colonoscopy starting 3-10 years post-operatively.[112,115]

DIFFERENCES IN RISK FACTORS FOR ADENOMATOUS VERSUS SERRATED POLYPS

There are important differences in the epidemiology of serrated class polyps and adenomatous polyps. Precancerous subtypes of serrated polyps (SSLs and traditional serrated adenomas [TSAs]) are less common than conventional adenomas. TSAs are quite rare, found in less than 1% of patients undergoing colonoscopy.[116] SSLs occur in roughly 15% of average-risk patients undergoing colonoscopy, when examinations are performed by high-detecting endoscopists.[116,117] In terms of nonmodifiable risk

factors, neither age nor male sex appears to be strongly related to prevalence of serrated lesions, in contrast to adenomatous polyps (see Fig. 1).[118]

However, white race is a risk factor for serrated polyps, particularly SSLs and microvesicular hyperplastic polyps.[65,118,119] With respect to modifiable risk factors, both smoking and alcohol intake appear to be more strongly associated with increased risk of serrated polyps compared with conventional adenomas.[59,120,121] Whereas supplemental calcium, vitamin D, and folate use have all been linked to decreased risk of conventional adenomas, some evidence suggests that these agents may actually increase the risk of serrated class polyps.[122,123] However, similar to conventional adenomas, both aspirin use and NSAID use are associated with decreased risk of serrated polyps.[65,89,123]

SUMMARY

The strongest nonmodifiable risk factors for CRC and precancerous polyps are age, male sex, and family history of CRC. Current evidence indicates that smoking, obesity, and diet are key modifiable risk factors for sporadic CRC. Unusual or uncommon CRC risk factors include acromegaly, HH, childhood cancer survivors, and patients who have undergone ureterosigmoidostomy. In contrast to adenomatous polyps, serrated polyp prevalence does not seem to vary much by age, and men and women appear to be at roughly equivalent risk. White race and smoking are stronger risk factors for serrated polyps than adenomatous polyps.

These data can be used to construct risk scores to identify persons at higher risk of advanced colorectal neoplasia and/or those who may benefit more from colonoscopy versus noninvasive CRC screening tests. Better knowledge of the epidemiology of colorectal polyps and cancer can also be useful in patient care, particularly when counseling patients regarding modifiable risk factors.

CLINICS CARE POINTS

- There is a 10% to 15% higher risk of adenomas in patients 70 to 75 years of age compared with the 50- to 55-year age group.
- Persons of black race and Alaskan native ethnicity have higher incidence of colorectal cancer compared with other races and ethnicities.
- Family history of colorectal cancer in first-degree relatives, particularly if family members are diagnosed under the age of 60 years, increases one's risk of both polyps and cancer.
- Diets high in red meat are associated with increased risk of precancerous polyps and colorectal cancer, whereas diets rich in intake of calcium, fiber, and fruits and vegetables are associated with lower risk.
- Patients with a history of childhood cancer (particularly with abdominopelvic radiation exposure), acromegaly, hereditary hemochromatosis, primary sclerosing cholangitis, and prior ureterosigmoidostomy surgery are at increased risk of colorectal cancer and therefore merit more frequent screening.
- The risk factor profile for serrated class polyps differs somewhat from that of adenomatous polyps, reflecting etiologic heterogeneity of colorectal cancer.

DISCLOSURE

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