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Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults

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Title: Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults

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Abstract

In contrast to the decreasing incidence of colorectal cancer (CRC) in older populations, the incidence has nearly doubled in younger adults since the early 1990s. Approximately 1 in 10 new diagnoses of CRC are now made in individuals 50 years or younger. Patients' risk of CRC has been calculated largely by age and family history, yet 3 of 4 patients with early-onset CRC have no family history of the disease. Rapidly increasing incidence rates in younger persons could result from generational differences in diet, environmental exposures, and lifestyle factors. We review epidemiologic trends in CRC, data on genetic and non-genetic risk factors, and new approaches for determining CRC risk. These may identify individuals likely to benefit from early screening and specialized surveillance.

Keywords: Colorectal cancer, early-age onset, epidemiology, risk factors

Colorectal cancer (CRC) incidence and mortality rates have changed substantially in the United States (US) over the past 4 decades. Incidence and mortality have each decreased among adults older than 50 years since the early 1990s.[1] These improvements are likely due to a combination of screening, shifts in distribution of risk factors (less smoking, more aspirin use), and improvements in treatment. However, data from epidemiology studies demonstrate an alarming and continued increase in CRC incidence among adults younger than 50 years.[2, 3] This early-onset CRC now accounts for 10-12% of all new CRC diagnoses. Little is known about the mechanisms of and factors that contribute to development of CRC in younger adults. Important questions to answer are: does early-onset CRC have distinct features from CRC that develops in older adults, and what environmental and lifestyle-related factors have contributed to increases in CRC incidence in younger, but not older, adults? Are there different risk factors for CRC in young vs old adults? We review the epidemiology and pathogenesis of CRC in young adults, including trends in incidence; genetic clinical, histopathologic, and molecular features; risk factors; and implications for screening.

Epidemiology

Trends in Incidence

After the adoption of population-based screening for CRC in the 1990s, CRC incidence has decreased in the total population by more than 35%.[4] Yet, in contrast to the great decreases among older adults, the incidence of CRC among younger adults has nearly doubled in the same time period.[2] Incidence rates have risen rapidly among persons ages 20–49 years in the US, from 8.6 per 100,000 in 1992 to 13.1 per 100,000 in 2016, with the largest increases among adults 40–49 years old.[4] Although CRC mortality has also decreased in older adults, largely due to screening and advances in treatment,[5, 6] mortality among younger adults has remained stable, at 2.8 per 100,000.[7]

Similar increases in early-onset CRC have been reported across the West, including Canada, Australia, and the United Kingdom (UK)., and in Asia. Despite overall population trends in aging, by 2030, approximately 11% of colon cancers and 23% of rectal cancers will occur in adults younger than age 50 years.[3]

In the US, rates of early-onset CRC vary widely by state (**Figure 1**). Rates are lowest (about 9.5 per 100,000) in western states and higher in the Mississippi Delta Region and Appalachia (about 14.0 per 100,000). Specifically, Mississippi and Kentucky have the highest incidence rates at 15.1 per 100,000 and 14.2 per 100,000, respectively. The Mississippi Delta and Appalachia are geographically diverse regions, characterized by poverty, unemployment, and poor access to healthcare. Incidence of all gastrointestinal cancers is higher in these regions compared to other parts of the US,[8] and CRC mortality rates (across age groups) are also strikingly high.[9] These geographic differences in incidence rates suggest environmental exposures (such as agricultural runoff, industrial pollution),[10] lifestyle-related factors (such as diet, obesity),[11] and/or occupational exposures (such as mineral dust, trace elements)[12] prevalent in these regions might contribute to pathogenesis.

Early-onset CRC has increased across successive birth cohorts (**Figure 2**),[2,13]—persons born in and after the 1960s are at higher risk of CRC when compared to older generations. For example, in the US, CRC incidence is higher among 40-year old persons born in 1970 (24.4 per 100,000) than 40-year old persons born in 1950 (18.3 per 100,000).[4] Interestingly, increases in early-onset CRC by birth cohort have also occurred worldwide, although risk varies by birth cohort within each country. In the US, incidence rates began to increase among *Baby Boomers*[2] and are highest among *Generation X*.[13] In Canada[14] and Australia,[15] the increased incidence of colon (vs. rectal) cancer was first noted among persons born in the 1970s. In Asian populations from Japan, Hong Kong, and Shanghai, increasing incidence rates appeared in later birth cohorts.[16] Birth cohort effects point to exposures

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occurring in early life, or exposures frequently experienced by younger generations, that may increase risk of early-onset CRC.[17]

Clinical features

Early-onset CRC is a challenge to study because most young adults diagnosed with CRC have no obvious risk factors (such as family history). In fact, most patients with early-onset CRC would be classified as average risk by current CRC screening and management algorithms. Age and family history of cancer remain the cornerstone of CRC risk stratification algorithms. However, only a minority of patients with early-onset CRC report having a first-degree relative with CRC, and even fewer have a predisposing condition (such as inflammatory bowel disease [IBD]).[18] [19, 20] Failure to consider the possibility of CRC, by patients and their providers, contributes to delays in diagnosis in younger adults – even in the presence of red flag symptoms (such as hematochezia or iron deficiency anemia). A substantial proportion of younger patients have metastatic disease at the time of diagnosis.

A higher proportion of younger patients have primary tumors in the distal colon or rectum compared with older patients, among whom proximal colon tumors predominate. Increasing incidence rates of early-onset CRC have been driven by increases in rectal (vs colon) cancer, particularly among whites.[21] Across all racial/ethnic groups, cases of rectal cancer increased by more than 90% from the early 1990s through 2016 (2.6 to 5.1 per 100,000),[4] compared to an increase of about 40% for cases of colon cancer. The largest relative increases in rectal cancer incidence have occurred in women (2.7 to 4.6 per 100,000). Differences in incidence by anatomic subsite indicate the importance of differentiating risk factors for colon vs rectal cancer.

Differences among races and ethnicities

Early-onset CRC disproportionately affects racial and ethnic minorities compared with non-Hispanic whites. Although 10%–12% of all patients diagnosed with CRC are younger than

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50 years, the proportion is nearly doubled among non-Hispanic blacks (16%) compared with non-Hispanic whites (9%).[22] Incidence rates of early-onset CRC have been persistently higher among blacks,[4] although the gap with whites has recently narrowed.[21] Incidence rates have also increased rapidly among young Hispanics.[23, 24]

Differences in survival by age of onset

Although most studies report no difference in CRC survival between younger and older patients with CRC, younger patients are more likely to be treated aggressively with surgery, multimodality chemotherapy, and/or radiation therapy.[25-29] Even among patients with stage 2 colon cancer, for whom guidelines recommend against use of adjuvant chemotherapy,[30] a large proportion of younger patients receive therapy.[31-34] Studies have found racial differences in survival times of younger adults diagnosed with CRC.[21, 35] Although these analyses are often limited by lack of detailed treatment information, blacks diagnosed with stage 2 CRC were 60% more likely to die of their disease compared with young non-Hispanic whites.[35] If younger patients with CRC have no survival advantage, despite more aggressive treatment, this could mean that young patients with lower risk-disease (limited nodal involvement, stage 2) are over-treated, or that young patients have tumors that are more aggressive and/or respond differently to treatment regimens developed for older patients with CRC.

Pathogenesis

Genetic factors

Among all age groups, germline variants in a number of genes are associated with increased risk for CRC (**Table 1**). As many as 10% of unselected patients with CRC carry germline variants in genes associated with high and moderate cancer susceptibility.[36] However, some of these variants have not been previously associated with CRC (such as *BRCA1, BRCA2, PALB2, ATM*, *NBN*, *CHEK2*, *BARD1*, *BRIP1*), and their role in pathogenesis and associated

risk are unclear. Genetic predisposition for early-onset CRC appears to differ from that of older-onset disease.

Specifically, younger patients have nearly double the prevalence (17%–35%) of pathogenic germline variants, and approximately half of these mutations are in DNA mismatch repair (MMR) genes associated with Lynch syndrome (**Figure 3**).[19, 37, 38] Population-based studies conducted in the US and Iceland estimate the population prevalence of Lynch Syndrome at approximately 1 in 279–300, and most individuals remain undiagnosed and unaware of their increased risk for cancer.[39, 40] Although universal testing of CRC tumors for MMR deficiency (MMRd) has been instrumental in identifying persons with Lynch Syndrome, tumor phenotypes vary—especially in patients with germline mutations in *MSH6* and *PMS2.* Constitutional MMR deficiency (CMMRd), resulting from biallelic germline mutations in MMR genes, has been implicated in development of CRC in very young patients (children and adolescents).[41]

Familial adenomatous polyposis, associated with germline mutations in *APC,* is perhaps the most easily recognizable of the hereditary syndromes. However, it is important to note that as many as half of patients with CRC found to have a pathogenic germline variant do not meet clinical diagnostic criteria for the corresponding hereditary syndrome.[19, 38] Although clinical practice guidelines deferred genetic testing for young patients without a family history or a polyposis phenotype, guidelines now recommend multigene panel testing of all young patients with CRC.[42]

Non-syndromic genetic factors

Multigene panel tests did not identify a germline mutation in approximately 80% of individuals with early-onset CRC. Whole-exome and whole-genome sequencing of large cohorts of patients with early-onset CRC have not identified common or rare genetic events associated with CRC with high penetrance. Genome-wide association studies are underway to investigate the potential impact of common variants associated with small (yet statistically

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significant) increases in CRC.[43-47] Modeling studies found that adding these common variants to CRC risk prediction models improved model performance compared to using family history alone.[48]

Molecular and histopathologic features

Large-scale tumor profiling initiatives have demonstrated that CRC is a heterogeneous disease. Although early-onset CRC is often underrepresented in large cohorts, including the Cancer Genome Atlas,[49] studies have found these cancers to have features that are distinct from those of older-onset, sporadic CRCs. Young adults diagnosed with CRC are more likely to have poorly differentiated tumors with features such as signet ring cell histology, lymphovascular invasion, and perineural invasion than older adults with CRC. Many of these features are associated with more aggressive tumors and worse prognosis.[20, 50] Although MMRd tumors are slightly more prevalent in patients with early-onset CRC, most tumors are microsatellite stable and have chromosome stability.

Analyses of colorectal tumors from multiple cohorts have identified striking differences in mutation and molecular profiles among patients with different ages of CRC diagnosis. Compared with tumors from older patients, few colorectal tumors from young patients have the somatic *BRAF* encoding V600E, whereas the prevalence of mutations in other genes involved in the MAPK pathway appears to increase with patient age.[18] Wnt pathway dysregulation is a common feature of non-hypermutated colorectal tumors, yet somatic mutations in *APC* are detected less frequently in early onset tumors compared to those from older patients.[51] Tumors from very young patients (younger than 30 years) have an increased prevalence of somatic mutations in *CTNNB1*.[18]

The prevalence of different tumor subtypes, based on molecular features, also appears to vary with age. The highest proportion of consensus molecular subtype-1 (microsatellite instability/immune) tumors are found in adults younger than age 40 years.[18] Although this molecular subtype encompasses hypermutated and MMRd tumors, it also

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includes neoplasms with markers of inflammation and/or the immune response. This observation supports the concept that longstanding colon inflammation contributes to their pathogenesis.

Epigenetic alterations, such as changes in DNA methylation patterns, have also been associated with early-onset CRC. Hypomethylation at long interspersed nuclear elements has been detected in a significantly higher proportion of tumors from young patients with non-hereditary CRC than from older patients. Hypomethylation at these elements has been associated with shorter survival times of patients with CRC and other cancers.[52, 53] The distinct molecular features of early-onset colorectal tumors indicates that they have unique mechanisms of pathogenesis. These features might be used in determining patient prognoses and selecting treatment.

Mechanisms of pathogenesis

The reasons for the increasing incidence of early-onset CRC are poorly understood. Differences in clinical presentation and tumor phenotypes raise the question of whether early-onset CRC is a different disease, with a different mechanisms of pathogenesis from CRC in older adults. Although family history and/or hereditary cancer syndromes account for some cases of early-onset CRC, lifestyle and environmental factors are also likely to contribute. Increases in incidence have occurred more rapidly than can be accounted for by changes in population genetics.[13]

Some risk factors have been associated with CRC at all ages (**Table 2**). These include obesity, smoking, alcohol, red or processed meat, non-steroidal inflammatory drugs (including aspirin), diet, micronutrients (such as calcium or vitamin D), physical activity, and chronic conditions (such as diabetes). Only a few studies have examined their effects on risk for early-onset CRC.[54-59] No study has examined the effect of diet, micronutrients, or non-steroidal inflammatory drugs, arguably some of the more important risk factors to study in early-onset CRC because their distribution in the population has shifted as incidence rates

have increased. It is therefore important to conduct population-based studies to identify lifestyle-related and environmental risk factors associated with early-onset CRC, informed by trends in incidence.

Birth cohort effects (see **Figure 2**) reveal the importance of reconsidering the timing and duration of well-established risk factors, such as obesity. Rather than assessing risk factors occurring in the few years before diagnosis, we might need to study these risk factors across a lifetime. Researchers have proposed that obesity might account for the increasing incidence of early-onset CRC.[60] However, only 10% of CRCs in all age groups can be attributed to obesity in adulthood.[61] Examining obesity during vulnerable windows of growth and development (such as birth weight[62] or childhood obesity[63, 64]) might provide more information on risk factors for early-onset CRC and identify periods of exposure that have the greatest effects on risk. Childhood obesity has increased by more than 200% since the early 1960s.[65-67] Although evidence is limited, studies have found a high body mass index (BMI) during childhood and/or puberty to increase risk of CRC.[64] Others have demonstrated a J-shape relationship between birth weight and subsequent CRC, whereby the lowest (<2000 g) and highest (>4000 g) weights are associated with CRC.[68]

Adult-onset obesity, which has a shorter latent period, might also contribute to risk. For example, weight gain during young adulthood (vs maintaining stable weight) is associated with a higher risk of CRC, and weight loss during this period is associated with lower risk.[69] Accumulating abdominal fat in adulthood appears to have a similar effect on risk.[70] A recent analysis of data from the Nurses' Health Study 2 reported BMI at age 18 years, as well as weight gain since adolescence, were associated with higher risk of early-onset CRC compared to normal body weight.[54]

The prevalence of chronic conditions associated with CRC, including type 2 diabetes[71] and IBD,[72] has increased in the U.S.,[73, 74] and there is some concern that these conditions now occur at a greater frequency in youth and young adults.[75, 76] For example, mean age at

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diabetes diagnosis decreased from 52 years in the late 1980s to 46 years in the early 2000s.[75] Incidence of pediatric-onset IBD has nearly doubled since the late 1980s.[76, 77] Eosinophilic gastrointestinal disorders have also increased during this period, [78] particularly among children and young adults. Increasing prevalence may be an artifact of changes in diagnostic criteria, but younger age at diagnosis may also reflect a true population trend in conditions marked by inflammation and injury. This is important because, at least in patients with IBD, the risk of CRC increases with duration, extent, and degree of colon inflammation,[79, 80] indicating an effect of altered immune regulation or surveillance. For persons with diabetes, prolonged exposure to hyperinsulinemia can shift the age-related acceleration in CRC incidence to an earlier age.[81] Only 1 study[59] has examined the association of early-onset CRC and diabetes; in a large population of Koreans undergoing colonoscopy examinations, those with younger than age 50 years and with type 2 diabetes had a modest increase in risk of CRC and advanced adenomas.

Among all age groups, studies[82-84] have found a reduced risk of CRC among physically active men and women, although the association appears stronger for colon cancer compared to rectal cancer. Risk reduction may occur through several mechanisms: less weight gain and body fatness, lower insulin levels and inflammation, and reduced transit time.[85] Prevalence of physical activity has remained consistent in the US over time (at about 25%),[86, 87] but sedentary behavior has increased, largely driven by deskbound working hours.[88] Evidence from the Nurses' Health Study 2 indicates that sedentary television viewing time (>14 hours per week) increases risk of early-onset CRC,[89] even after adjusting for confounding effects of physical activity, BMI, and smoking.

Possible risk factors

Although not specific to early-onset CRC, several prospective cohort and case-control studies have associated antibiotic use with advanced adenomas[90] and CRC (in all age groups[91, 92]), mediated by their effect on gut microbiota. The human intestine contains a

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diverse community of microbes that affect health.[93] Diet and environmental exposures

determine their diversity, and alterations in microbiota induce changes in gene

expression, metabolism, and local and systemic immune responses.[94] In the US, use of

broad-spectrum antibiotics nearly tripled through the 1980s,[95] due to inappropriate

prescriptions for ear and upper respiratory infections in children.[96] Antibiotics given at weaning

to mice increase adiposity and alter the composition of intestinal microbiota.[97] Other studies

show even small doses of antimicrobial agents affect the microbiota. For example, brief

exposure to triclosan, an antimicrobial agent added to hundreds of consumer products in the

1970s,[98] causes inflammation, increases colitis, and exacerbates colitis-associated cancer in

mice.[99]

Beyond antibiotics, other dysbiosis-related factors, such as periodontal disease,

modestly increase risk of CRC, so pathogens might be involved in carcinogensis.[100] Mucosal

colonization with specific pathogens (including *fusobacterium nucleatum*) has been

associated with CRC risk, and other organisms might modify risk, either individually or in

aggregate.[101] We have only recently begun to understand the complexity of intestinal

microbiota, but studies of microbiota-related risk factors might increase our understanding of

early-onset CRC.

Risk factors more strongly associated with rectal cancer and increasing in prevalence

are likely to contribute to development of early-onset CRC. Studies that examined the risk of

colon and rectal cancer separately found that family history, obesity, physical activity, and

smoking had different effects on risk.[102, 103] The reasons for these differences are poorly

understood. Concentrations of bile salts and metabolites, level of oxygenation, and microbial

environments vary along the colorectum.[104] These might affect susceptibility to risk factors and

create better or worse conditions for carcinogenesis.[105] There are different embryonic origins

of the proximal (midgut) colon and distal (hindgut) colorectum,[106] which might also affect

carcinogenesis. For example, the right colon is exposed to bile acids and other metabolites

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that have escaped the small intestine, and in a form that the left colon is not, after bacterial action on metabolites. Unrecognized toxins, either dietary or environmental, might also have systemic and/or local effects on rectal mucosa.

Studies of racial and ethnic differences in the prevalence of risk factors might provide additional insights into development of early-onset CRC. For example, blacks have more constant exposure to type 2 diabetes[75] and childhood obesity[67] compared with the increases in exposure that have only recently occurred among whites. Young Hispanics have a greater burden of other gastrointestinal cancers (such as liver or gastric cancer) compared with non-Hispanic whites,[107] and shared risk factors among these cancers, such as metabolic syndrome,[108] could account for the rapidly increasing incidence rates. Immune responses and inflammation differ among races and ethnicities (stronger lymphocytic reactions in tumors of African Americans[109]). Monitoring changes in the relative presence or absence of risk factors and differences in tumor molecular phenotypes by race/ethnicity will increase our understanding early-onset CRC, particularly as the demographic landscape of the US continues to evolve.

Despite evidence supporting the association of lifestyle-related risk factors with early-onset CRC, case studies have shown that many young adults with CRC led previously active and healthy lives. Studying risk factors not traditionally considered to be associated CRC, or with limited evidence (**Table 2**), could provide additional clues of pathogenesis. For example, given the number of microbes found in the colorectum, infectious agents (such as human papillomavirus or *Helicobacter pylori*) associated with other types of cancer might also contribute to early-onset CRC.[110] Other microbiota-related events, such as cesarean delivery, pre- and perinatal antibiotics, or breastfeeding could create an imbalance of infants' microbiome[111] that affect susceptibility to CRC in young adulthood. These factors[112] have also increased among generations at higher risk of early-onset CRC.[113] Finally, some have

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suggested environmental toxins may be related to early-onset disease, although evidence is still very limited.[114]

Treatment and Prevention

Reducing incidence

Because CRC screening has demonstrated benefits for older adults (age >50 years),[115] the American Cancer Society recently recommended lowering the age to initiate screening to 45 years.[116] In addition to simulation modelling, the American Cancer Society based its recommendation on the observation that CRC risk among persons 45–49 year old is now similar to that of persons 50–54 years old in the early 1990s. The implications of widening the age-eligible screening pool has generated controversy for several reasons. It is important to recognize that the large relative increase in early-onset CRC corresponds to a smaller absolute increase in incidence.[117] Incidence increased by 30% among 40-year old persons from 1992 to 2015, and the absolute difference in incidence rates over the same period is only 8.2 cases per 100,000. It has been estimated that lowering the screening age will result in an additional 22 million persons eligible, overwhelming endoscopic capacity, incurring substantial costs, and perhaps diverting resources away from older adults more likely to benefit.[118-122] We lack empirical data supporting the efficacy of screening younger adults; most of the landmark screening trials are limited to adults older than 50 years. This makes it difficult to determine expected benefits and harms, yield, and test performance. Earlier screening may exacerbate disparities because younger adults most likely to be screened (health-seeking and early adopters) are also unlikely to belong to racial/ethnic and socioeconomic subgroups at higher risk.[121] Finally, half of persons with early-onset CRC are younger than age 45 years, so lowering the screening age will provide little or no benefit to these patients.

Improving risk assessment

Because we lack evidence on the benefits and harms of initiating screening at age 45 years (vs 50 years), we should instead focus on improving how we define persons at higher risk. Precision cancer screening uses a combination of genetic factors, environmental and lifestyle exposures, and prior screening to determine the expected benefit of screening for any individual person.[123] Better risk assessment – and personalized screening regimens based on risk – may improve the ratio of benefit to harm over conventional age-based screening strategies. For example, risk prediction models[43, 124] that include information on genetics and environmental risk factors determine the starting age for screening with greater accuracy than models including family history or age alone. The starting age in these models ranges from 38 years for men with a family history of CRC and higher risk score to 71 years for women with no family history and lower risk score.[124] Risk prediction models may also inform choice of screening test (such as colonoscopy vs FIT).[125] For example, because younger adults have proportionately more left-sided cancers, stool-based tests or sigmoidoscopy may be an appropriate, less invasive option. As genetic data become increasingly available, and we learn more about environmental risk factors of early-onset CRC, we will have opportunities to develop and validate risk prediction models that expand precision screening efforts. In the meantime, improving recognition of family history (of CRC and advanced adenomas), [126-128] IBD, and red flag symptoms may facilitate earlier screening for individuals at higher risk of early-onset CRC.

Future Directions

Incidence rates of early-onset CRC have increased in the US and across much of the West since the 1990s, for unknown reasons. Although genetic factors can affect risk of early-onset CRC, most young adults diagnosed with CRC have no hereditary syndrome or germline mutation associated with CRC,[19] and traditional clinical criteria (family history, tumor phenotype) fail to identify those at higher risk.[129, 130] Many patients lack the classic family

history or disease phenotype and/or have genetic mutations that have not been associated with CRC.[129]

Genetic testing of all patients diagnosed with early-onset CRC could guide treatment and facilitate testing and earlier cancer screening for at-risk relatives. Beyond genetic factors, increases in incidence by birth cohort indicate that environmental and lifestyle-related risk factors, particularly exposures during early life, contribute to early-onset CRC. Further studies of genetic and molecular features of colorectal tumors, as well as the effects of exposures on colorectal mucosa, will provide additional information about carcinogenesis and new treatment approaches.

Figure Legends:

Figure 1. Incidence rates of early-onset CRC (ages 20-49 years) by US state, National Program of Cancer Registries, 2001 – 2015

Figure 2. Incidence rate ratios for CRC by birth cohort

Figure 3: Prevalence of pathogenic variants by age at CRC diagnosis. Based on findings reported in [19, 36, 37, 131]

Figure 3 (continued): Genes that contain pathogenic variants by age at CRC diagnosis

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Table 1. Genes containing variants associated with CRC risk

Genes	Hereditary Syndrome	Penetrance[1]	Population Prevalence	Proportion of CRC (all ages)	Lifetime risk of CRC
DNA mismatch repair (*MLH1, MSH2, MSH6, PMS2, EPCAM)*	Lynch syndrome	High	1 in 279	3%	25-75%
APC	Familial adenomatous polyposis	High	3 in 10,000	1%	90-100%
MUTYH	*MUTYH*-associated polyposis (biallelic autosomal recessive)	High	1 in 100	1%	40-90%
	Monoallelic *MUYH*	Low	1 in 100	3%	5-10%
SMAD4, BMPR1A	Juvenile polyposis	High	1 in 100,000	<0.1%	36-68%
PTEN	Cowden/ multiple hamartoma syndrome	High	1 in 200,000	<0.1%	9-16%
STK11	Peutz Jeghers syndrome	High	1 in 50,000 – 200,000	<0.1%	39%
POLE, POLD1	Polymerase proofreading associated polyposis	High	Unknown	<0.1%	Unknown
NTHL1, MSH3	Autosomal recessive polyposis	Moderate/high	Unknown	<0.1%	Unknown
TP53	Li Fraumeni syndrome	High	1 in 5,000 – 20,000	<1%	10-20%
CHEK2		Moderate/low	2 in 100	<1%	5-10%

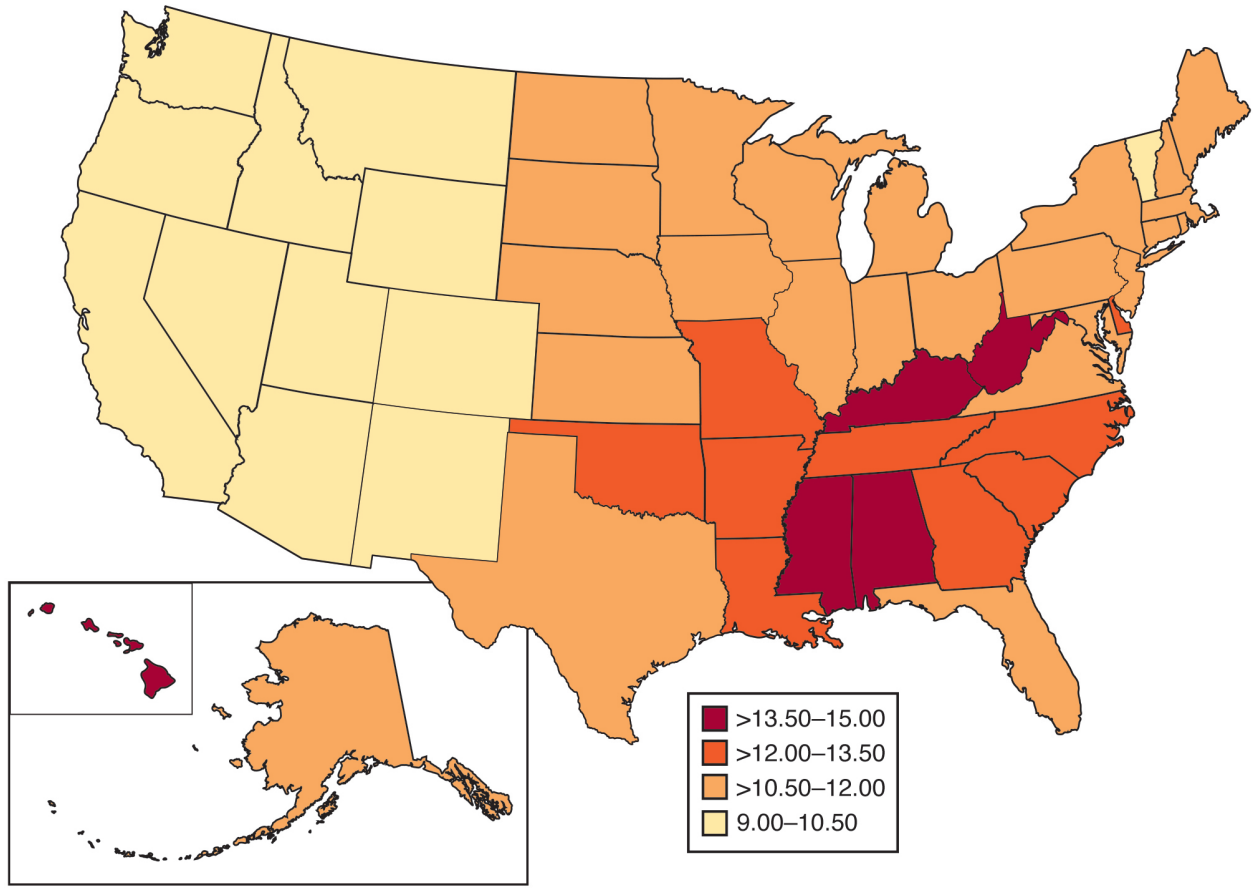NOTE: Based on findings reported in [19, 36, 37, 131, 132]

[1]High-penetrance corresponds to an increase in risk of cancer (any type) that is 4 times the general population[133]
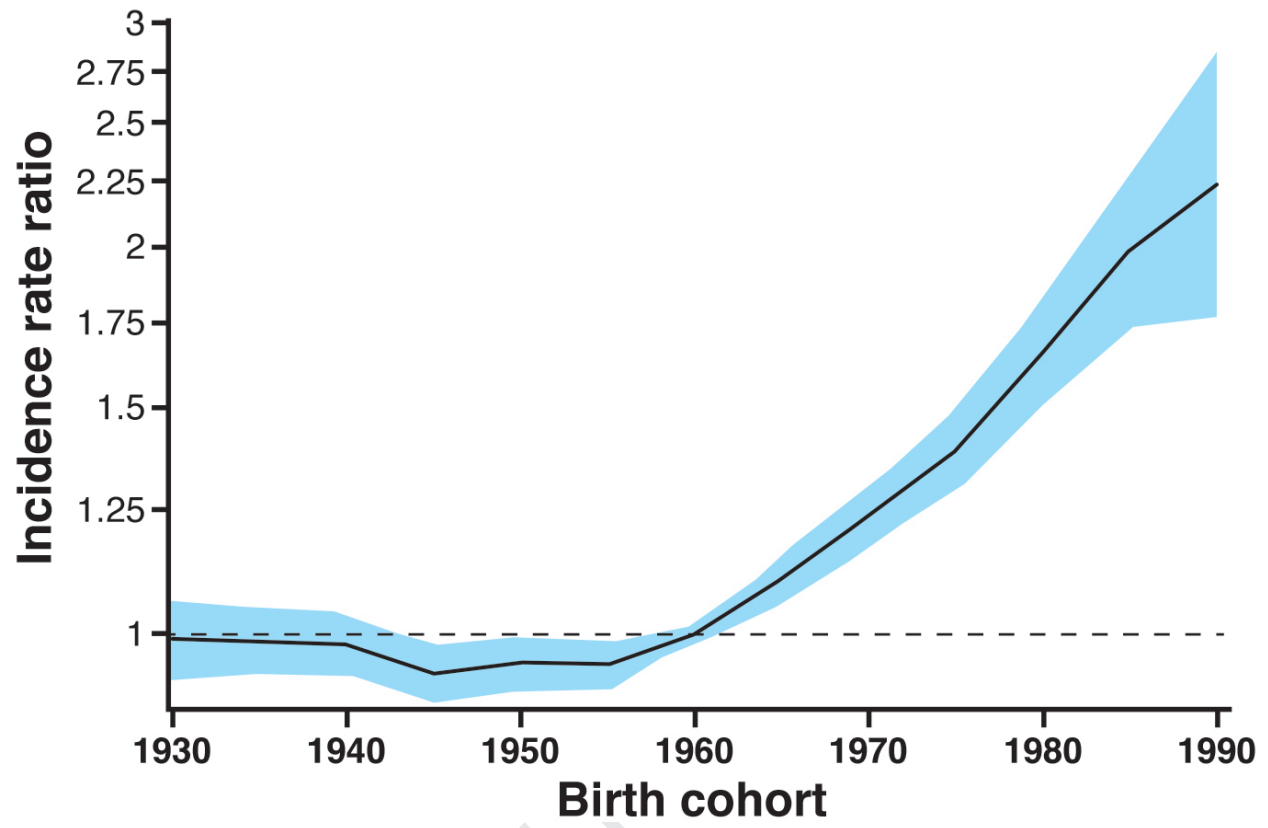
Table 2. Lifestyle-related and environmental risk factors associated with CRC and relationship with early-onset disease

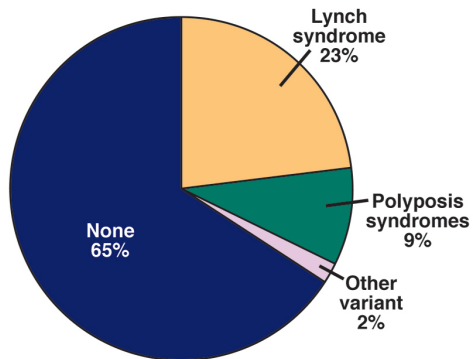| Risk factor (direction of risk)	Hypothesized mechanism	Supporting evidence	Studied in early-onset CRC?
Established risk factors			
Obesity (+)	Metabolic syndrome; insulin resistance; chronic inflammation; altered levels of adipocytokines[134]	Meta-analyses show association between adiposity (including measures of body mass index, waist circumference, and waist-to-hip ratio) and CRC[60, 135, 136]	See ref. [54, 59]
Smoking (+)	Direct ingestion of or indirect exposure (via circulatory system) to known carcinogens contained in tobacco products[137]	Meta-analyses demonstrate association between cigarette smoking and CRC incidence and mortality,[138, 139] as well as risk of adenomas[140]	See ref. [59]
Alcohol (+)	Consumption adversely affects folate metabolism; genotoxic effects of acetaldehyde[141]	Meta-analyses of cohort and case-control studies report moderately increased risk of CRC associated with alcohol consumption[142, 143]	See ref. [57]
Red or processed meat (+)	Consumption induces N-nitroso-compound formation; contains heterocyclic aromatic amines and polycyclic aromatic hydrocarbons, known carcinogenic chemicals[144]	Prospective cohort and case-control studies demonstrate CRC associated with high vs. low consumption of red and processed meat[145, 146]	See ref. [57]
Aspirin/ NSAID (-)	Inhibits cyclooxygenase and phospholipase activity, enzymes involved in tumor growth and intracellular signaling[147]	Decreases incidence of CRC[148] and adenomas[149] in randomized trials conducted in U.S. and Europe	--
Dietary patterns (+)	Synergistic effect of highly correlated nutrients and other compounds in food, including vitamins, carotenoids, calcium, and folate; chronic inflammation[150]	Some studies show "western" diets (more processed foods, sugar, fat, and refined grains) increase risk,[151-153] although findings are inconsistent across all studies	See ref. [154]
Micronutrients (-)	Calcium inhibits carcinogenic effects of bile acids in colorectum; Vitamin D lowers risk via antiproliferative, pro-apoptotic, and anti-angiogenic properties[155]	Calcium[156] decreases incidence of colorectal adenomas in randomized trials; inconsistent evidence supporting effect of vitamin D or folate	--
Physical activity (-)	Less weight gain and body fatness; lower insulin levels and inflammation; stimulate digestion and reduce transit time[85]	Prospective cohort and case-control studies show reduced risk of colon cancer among physically active men and women;[82, 83] fewer data support association with rectal cancer[103]	See ref. [89, 157]
Diabetes (+)	Insulin resistance; chronic insulin therapy; shared risk factors (e.g., obesity); elevated concentration of fecal bile acids[71]	Meta-analyses of case-control and cohort studies demonstrates 30% increase in CRC risk among those with type I and II diabetes[71, 158]	See ref. [59]
Inflammatory bowel disease (+)	Chronic inflammation and altered immune response; oxidative stress; microbiota-induced carcinogenesis[159]	Large cohort studies report increased risk of CRC among persons with IBD; risk increases with duration and severity of symptoms[160]	--
Other possible risk factors			
Antibiotics (+)	Alters patterns of microbiota assembly;[161-164] may give rise to biological pathways initiating or promoting CRC[97, 165, 166]	Antibiotic use in adults associated with increased risk of CRC (ages ≥50 years) in U.S.[90] and European[91, 92] studies	--

2

Birth weight (+)	Pregnancy hormones (e.g., growth and steroid hormones, insulin) associated with birth size;[68] large birth size associated with increased risk of obesity in adulthood[167, 168]	Prospective cohort studies in Nordic countries report association between birth size and CRC[68, 169, 170]	--
Childhood obesity (+)	Increased body fatness in childhood and adolescence associated with higher insulin levels;[171] obesity in childhood correlated with body fatness in adulthood[172]	Early life body fatness increases risk of CRC in large, prospective cohort studies[63, 173]	See ref. [54]
Cesarean delivery (?)	Thwarts vertical transmission of vaginal and gut microbiota from mother to infant[111, 174]; delivery by C-section increases risk of metabolic diseases[175] and obesity[176]	--	--
Breastfeeding (?)	Initial breastfeeding reduces risk of obesity later in life;[177] influences composition of infant microbiome[178]	--	--
Infectious agents (?)	Colon is frequently exposed to both pathogenic and non-pathogenic viruses, including H. pylori, HPV, and JC virus	Inconsistent evidence support the effect of infectious agents on risk of CRC (reviewed in [110])	--

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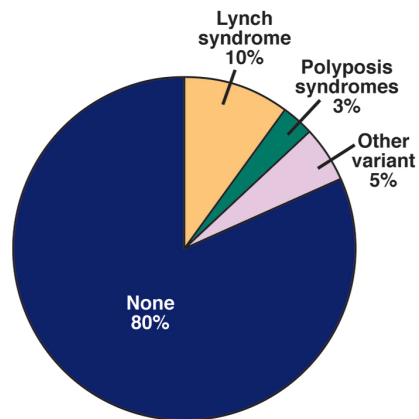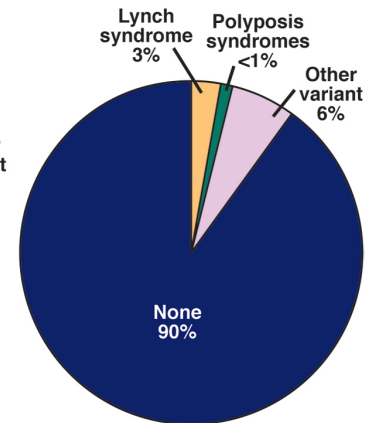>12.00–13.50
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Age <35 years

Lynch
syndrome
23%

Polyposis
syndromes
9%

Other
variant
2%

None
65%

Age <50 years

Lynch
syndrome
10%

Polyposis
syndromes
3%

Other
variant
5%

None
80%

Age >50 years

Lynch
syndrome
3%

Polyposis
syndromes
<1%

Other
variant
6%

None
90%

Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	APC	BRCA1	CHEK2
MSH2	MUTYH	BRCA2	ATM
MSH6	SMAD4	TP53	NBN
PMS2	BMPR1A	PALB2	BARD1
	PTEN	CDKN2A	BRIP1
	POLE		