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## Young-onset colorectal cancer: A review

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### Abstract

Despite the general decrease in overall incidence of colorectal cancer since the early 1990s, the incidence of colorectal cancer in patients less than 50 years old has nearly doubled. A systematic review was performed using the PubMed database (2011-2020) and Cochrane Database of Systematic Reviews (2011-2021) to identify studies (published in English) evaluating epidemiologic, clinical, hereditary, and molecular features; as well as evaluation, management, and prognosis of young-onset colorectal cancer patients. Our search yielded a total of 3401 articles, after applying our inclusion criteria. We fully reviewed 94 full-length studies. This systematic review demonstrates the increasing incidence of young-onset colorectal cancer and highlights the importance of being hypervigilant for the differential diagnosis colorectal cancer when evaluating a young adult who presents with gastrointestinal symptoms.

**Key Words:** Young-onset colorectal cancer; Early-onset colorectal cancer; Colorectal cancer; Genetic; Young adult; Hereditary

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**Core Tip:** Despite the overall decreasing incidence of colorectal cancer, the incidence of young-onset colorectal cancer is on the rise. Identifying genetic, molecular, clinical, behavioral patient characteristics of this subset population is vital in the timely diagnosis and customized management of these patients.

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## INTRODUCTION

The introduction of screening colonoscopy has led to the prevention and decrease in overall incidence of colorectal cancer (CRC) since the early 1990s. In contrast, the incidence of CRC in young patients has continued to steadily increase annually. Within the last 10 years, patients diagnosed with CRC at age younger than age 50 years have defined a cohort of patients known as young-onset or early-onset CRC. Young-onset CRC (or “early-onset” CRC) generally refers to CRC occurring in patients under 50 years old, who until recently did not meet traditional age criteria for average-risk screening in the United States. This finding is alarming for several reasons. Firstly, this population of patients is not captured by routine CRC screening due to the conventional recommendation that CRC screening start at the age of 50. Secondly, as we have come to characterize this subset of young patients in the last decade, younger CRC patients have been shown to present with more advanced stages of CRC and the concern encompasses not only a delay in diagnosis, but also whether there are multifactorial genetic and environmental components that characterize this cohort of young CRC patients. In this systematic review, we discuss the epidemiology, risk factors, clinical presentation, evaluation, treatment, and hereditary, genetic and molecular features of early-onset CRC. This data will inform future implications in the debate over the appropriate age for the initiation of screening and the utilization of precision medicine to customize management of young patients with CRC.

## METHODLOGY

A systematic literature search was conducted by two independent reviewers. The PubMed database was searched from the last 10 years, from February 15, 2011 through November 13, 2020 and the Cochrane Database of Systematic Reviews, from February 20, 2011 through February 20, 2021. Key word combinations using the MeSH terms included “early-onset colorectal cancer,” “young-onset colorectal cancer,” “young,” “colorectal neoplasm,” and “colorectal cancer.” The search was limited to English language with human subjects. Emphasis was placed on prospective trials, meta-analyses, systematic reviews, and practice guidelines. A total of 3364 PubMed journal titles were identified and 94 titles underwent full-length article assessment. A total of 37 Cochrane reviews matching MeSH descriptors of “colorectal neoplasms” were reviewed. Additional relevant manuscripts and other media-based material identified by the manuscript’s authors were also included in this systematic review.

## EPIDEMIOLOGY

CRC is currently the fourth most common cancer among men and women in the United States, with approximately 147950 new cases diagnosed each year[1]. The overall incidence rate of CRC has declined significantly in the last four decades[2-4]. Colonoscopy, the mainstay modality of CRC screening, allows for the detection and removal of polyps in the colon before they develop into cancer. Interrupting the adenoma-carcinoma sequence has largely been credited in lowering the incidence rates of CRC in adults over age 50. In contrast, for patients under age 50, there has been an increase in the incidence rate of CRC[5]. When analyzing CRC incidence *via* the Surveillance, Epidemiology, and End Results (SEER) data from 1974-2013, adults ages 20 years to 39 years were noted to have a 2.4% annual increase in CRC incidence rates, while adults ages 40 years to 49 years had a 1.3% annual increase in CRC incidence in the mid-1990’s. Between 2012 and 2016, there was a 3.3% annual decline in incidence rates of CRC among those greater than age 65. Among those under age 50, there was a 2.2% annual increase in incidence rate of CRC for patients under 50 during the same period, with the greatest increase in CRC incidence rates seen among patients between ages 20 to 34[6]. Among adults under the age of 50, CRC is now the second most common cause of cancer among men, and the fourth most common among women) [7]. Recent estimates suggest that by 2030, the incidence rate of colon cancer among

this group will increase by 90%, and the incidence rate of rectal cancer in this group will increase by 124.2% [2]. A greater proportion of the increases in CRC is attributable to increases in rectal cancers compared to proximal colon cancers, with an increased annual incidence rate of 3.2% in adults ages 20 to 39 and 2.3% per year beginning in the 1990s in adults ages 40-49 [8]. It is estimated that by 2030, roughly 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in patients under age 50 [3]. Although CRC mortality rates have decreased among older adults, mortality among those under 50 appears to be gradually increasing, with an estimated 1.9 deaths per 100,000 as of 2018 [4]. International trends mirror these aforementioned US trends and have been reported across the West, including Canada, the United Kingdom, Sweden, Switzerland, Italy, as well as Australia, Egypt, and in Asia [2,9-13].

There are substantial differences in CRC incidence among racial and ethnic groups in the United States [14]. A study using the California Cancer Registry examining trends in incidence of CRC in the largest state with the most diverse racial and ethnic population found that 21% of South Asians and 20% of Southeast Asians were under age 50 at diagnosis, compared to 8.6% of non-Hispanic whites and Japanese. Two thirds of patients under age 50 at diagnosis were found to have late-stage (regional or distant disease) at diagnosis. The study also found that non-Hispanic Black Americans are disproportionately diagnosed with a great prevalence of CRC, later stages of disease, and poorer overall survival rates [15,16]. Compared to non-Hispanic whites, non-Hispanic black Americans had a 40% higher incidence of late-stage disease. And while declines in CRC were seen between 1990 to 2014 in the overall population, Southeast Asian (Filipino, Vietnamese, Thai, Hmong, Cambodian, and Laotian) groups had an increased incidence rate of CRC during this same period [17].

In the United States, the incidence rates of young-onset CRC vary by state. Western states demonstrate the lowest rates of early-onset CRC (9.5/100,000), while the Mississippi Delta Region (Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, Tennessee) and Appalachia demonstrate the highest rates, with 15.1 and 14.2 cases per 100,000 respectively. Common to the Mississippi Delta and Appalachia are poverty, unemployment, and poor access to healthcare [1]. Mortality rates in these “hotspots” for all-comers with CRC is high [18].

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## RISK FACTORS FOR YOUNG-ONSET CRC

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The strongest known risk factor for CRC is a family history of the disease. It has been estimated that approximately 23-39% of patients with young-onset CRC have a family history of CRC [19-21]. People with a first-degree relative diagnosed with CRC have two to four fold increased risk of CRC, and this risk increases with a younger age at diagnosis [22,23]. A family history of adenomas in multiple affected relatives (first-degree relatives and distant relatives) also increases the risk of developing CRC [24]. A study by the Ohio Colorectal Cancer Prevention Initiative evaluated all CRC patients undergoing surgical resection for microsatellite instability *via* immunohistochemistry, as well as performing germline genetic testing for 25 cancer susceptibility genes. Sixteen percent were found to have a hereditary syndrome of which half were also found to have microsatellite instability (Lynch syndrome) [25]. Although a larger proportion of young-onset CRCs are hereditary compared with CRCs occurring in the older population, 75% of young-onset CRCs are sporadic and occur in patients with no family history of CRC [1,20].

Globally, the increase in CRC incidence among young patients is attributed to a strong birth cohort effect [26]. A birth cohort effect occurs when age-specific incidence rates vary by age group due to a change in exposure (behavioral, cultural, lifestyle, and environmental factors) that influences disease risk [8,26]. Obesity, diabetes, lack of physical activity, heavy alcohol consumption, and a typical “Western” diet (rich in fast food, processed and red meat, and poor intake of vegetables and fruits), are associated with increased risk of CRC [1,9,10,27-35]. The prevalence of obesity has increased in the United States, and there is evidence of an association between obesity and risk of developing CRC prior to age 50. A national longitudinal study evaluating 12.6 million Swedish residents between 1964 to 2015 to investigate how many years earlier patients with diabetes reach the 10-year cumulative risks of CRC as a 50 years old man or woman without diabetes demonstrated that diabetic patients attained the screening level of CRC risk 5 years earlier [9]. Sedentary behavior has increased as a result of a greater number of desk-bound work hours and passive media consumption, and there is evidence that sedentary behavior independently increases risk for young-onset CRC after adjusting for the effects of obesity and physical activity [36]. A comparative

analysis between patients ages 20-39 with CRC and the same age group in the general population without CRC shows that young patients with CRC have higher prevalence rates of medical comorbidities, such as diabetes, smoking and obesity[37]. The causal relationships between behavioral factors and the increasing incidence of CRC among young patients are not established.

Inflammatory bowel disease (IBD) is also a risk factor for CRC and increases the risk of CRC by two- to three-fold[38,39]. Young-onset CRC patients with IBD are more likely to have mucinous or signet ring histology and less likely to have APC mutations [40].

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## CLINICAL PRESENTATION

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Patients with young-onset CRC are more likely to be Caucasian and female. Although CRC is often asymptomatic, red-flag symptoms such as unexplained anemia, rectal bleeding, and changes in stool caliber may herald CRC. Predominant presenting symptoms in young-onset CRC patients include rectal bleeding/hematochezia, change in bowel habits, abdominal pain, anemia, decreased appetite, and weight loss[37,41-43]. According to the literature, there is a 7 wk to 2-year delay in diagnosis of CRC in adults under the age of 50[21,41,43]. This is thought to be due to a low level of suspicion for CRC by clinical providers who assume a benign diagnosis, such as irritable bowel syndrome, or treat/refer for anorectal evaluation (*e.g.*, hemorrhoids) rather than diagnostic endoscopy[43]. Other factors that contribute to delay in diagnosis in younger adults include a sense of invincibility, fewer financial resources, and often a lack of medical insurance[44].

Young-onset CRCs have distinct clinical and pathologic characteristics compared to typical CRCs occurring in older adults. Young-onset CRCs are less likely to have an associated precursor adenomatous lesion[37], and are more likely to occur distal to the splenic flexure or rectum[21,33,37,43]. Left- and right-sided colon cancers have different molecular features, responses to biologic therapies[45], and prognoses[46]. Compared to older patients, young-onset CRCs appear to be diagnosed at later stages (with nodal or distant metastases at presentation)[20,33,43,47,48], are more frequently diagnosed with synchronous or metachronous cancers[49], and are more likely to develop metastatic disease during their disease course[40,50]. This may be partially explained by the fact that multiple different medical societies' current screening guidelines do not recommend screening in patients younger than 50 unless there is a known family history or other specific risk factors.

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## SCREENING RECOMMENDATIONS

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In May 2018, the American Cancer Society (ACS) published guidelines recommending CRC screening for average-risk adults beginning at age 45[51]. More recently in late 2020, the US Preventive Services Task Force (USPSTF) expanded its recommendations for CRC screening guidelines to include adults age 45-49[52]. The ACS and USPSTF do not make specific screening recommendations for higher-than-average risk individuals. For those who have a family history of CRC, the US Multisociety Task Force on Colorectal Cancer recommends initiation of screening 10 years prior to the age of diagnosis of the youngest affected relative or age 40, whichever is earlier[53]. These recommendations for CRC screening in patients younger than age 50 are based on a paucity of evidence for CRC screening in asymptomatic adults and rely heavily on modeling studies, due to the fact that most observational studies evaluate young adults receiving colonoscopy because of symptoms, family history, and reasons other than screening[54] (Table 1).

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## EVALUATION AND TREATMENT

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Regardless of age of onset, per the American Society of Colon and Rectal Surgeons, prior to initiating treatment, patients who have not had a full colonoscopy prior to diagnosis of their CRC should undergo a full evaluation of the colorectal mucosa with a colonoscopy to detect the presence of synchronous lesions. In patients who are unable to undergo preoperative colonoscopy, postoperative colonoscopy can be performed 3 months after resection of the tumor. An assessment of carcinoembryonic

**Table 1 Recommendations for colorectal cancer screening across professional organizations[54]**

Professional organization	Recommended ages for screening	Recommended screening tests	Other considerations
U.S. Preventive Services Task Force (2016)	50-75	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	
U.S Multi-Society Task Force on Colorectal Cancer (2017)	50-75	FIT, colonoscopy (Tier 1) <sup>1</sup>	Screening at age 45 yr for African Americans; AGA endorses Canadian guidelines on screening in setting of family history
National Comprehensive Cancer Network (2018)	50-75	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	Focused guidelines address screening for high-risk syndromes
American College of Physicians (2012)	50-75	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy, DCBE	
Canadian Task Force on Preventive Health Care (2016)	50-74	gFOBT, FIT, sigmoidoscopy	Weak recommendation for screening in ages 50-59 yr
American Cancer Society (2018)	45-75	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	Qualified recommendation for initiating screening at age 45 yr – uncertainty regarding ratio of benefits to harms

Modified from Murphy[54].

<sup>1</sup>Tier 2 tests include computed tomography colonography, fecal immunochemical tests-DNA, flexible sigmoidoscopy.

gFOBT: Guaiac-based fecal occult blood tests; FIT: Fecal immunochemical tests; CT: Computed tomography; AGA: American Gastroenterological Association.

antigen (CEA) level is obtained prior to elective surgery and establishes a baseline value for which to assess for recurrence during the surveillance period.

Preoperative staging of CRC using computed tomography (CT) of the chest, abdomen, and pelvis is recommended to establish a baseline for which to assess for recurrence during the surveillance period. Magnetic resonance imaging (MRI) of the abdomen may be obtained in patients with significant contrast allergy or renal disease. Positron emission tomography/CT (PET/CT) may be selectively used in patients with unexplained elevation in CEA, or when there is suspicion for local recurrence of CRC. Otherwise, routine use of PET/CT for CRC staging is not recommended[55].

Pelvic MRI is employed in rectal cancer staging to characterize tumor (T) stage, lymph node status, and adjacent organ involvement of the rectal cancer. Endorectal ultrasound (ERUS) is indicated when MRI pelvis is contraindicated, inconclusive, or when there is need for further evaluation of superficial lesions[56].

For patients with young-onset CRC, most patients require segmental resections (95%), with a smaller proportion requiring subtotal or total colectomy[43]. Pathology of patients with young CRC more frequently display aggressive histologic characteristics such as poor differentiation, signet ring cell differentiation, perineural invasion, and venous invasion, and in rectal cancer, young-onset CRCs are more likely to have a positive circumferential resection margin (CRM)[48,57]. Although CRM is an independent prognostic factor in rectal cancer[58], there is evidence that younger patients do not experience worse recurrence-free or overall survival compared to their older counterparts[59,60], with some studies suggesting that young patients have greater survival at every stage of disease compared to their older counterparts[58]. Current guidelines for therapy in CRC are driven by results of clinical trials with predominantly older patients. However, a study of the impact of age and stage-appropriate National Comprehensive Cancer Network (NCCN) guideline-driven care in rectal cancer demonstrated that although younger patients benefited from NCCN guideline-driven care in stage I disease (surgical resection alone), there was no survival benefit for guideline-concordant care in stage II and III disease (neoadjuvant chemoradiation, surgical resection, and systemic chemotherapy)[56]. In fact, a subset analysis showed that for stage II and III rectal cancer, NCCN guideline-driven care led to reduced survival in patients under 45, and a survival benefit only for those older than 54[61]. These findings suggest that young-onset rectal cancer may differ in biology and response to therapy compared to rectal cancer occurring in older patients.

There is evidence that after adjusting for patient- and tumor-related factors, younger patients receive more aggressive adjuvant treatment, particularly with respect to multi-agent systemic chemotherapy and local irradiation, when compared to their older counterparts[47,58]. Young-onset rectal cancer patients are more likely to receive

radiotherapy at all stages of disease. Young-onset CRC patients with distant metastasis are more likely to receive surgical therapy for their primary tumor[58]. Because of higher rates of recurrence and progression and metachronous cancer development risk, postoperative surveillance is important in young patients[43,49].

## OTHER CONSIDERATIONS

### Referral to genetics counselor

Across all age groups, germline mutations in a number of genes are known to be associated with an increased susceptibility to CRC, and these include mutations in mismatch repair (MMR), as well as *BRCA2*, *BMPRI1A*, *SMAD4*, *BRIP1*, *PALB2*, *GREM*, *POLE*, *SMAD4*, *NF1*, *ATM*, *NBN*, *CHEK2*, *BARD1*, *SRC*, *TP53*, *PTEN*, *STK11*[13,62,63]. Young-onset CRC patients have fewer *BRAF* V600 mutations[64,65] and adenomatous polyposis coli (APC) mutations compared to their older counterparts[40].

One study comparing mutational profiles of left-sided CRCs have found that younger patients had higher rates of mutations in known genes associated with cancer-predisposing syndromes, such as *MSH2* and *MSH6* (hereditary nonpolyposis CRC, HNPCC or Lynch syndrome), *NF1* (neurofibromatosis type 1), *PTEN* (hamartoma tumors syndrome or Cowden's syndrome), *TSC1* and *TSC2* (tuberous sclerosis complex), and *BRCA2* (hereditary breast and ovarian cancer syndromes)[66]. Using next-generation sequencing, the study found that TMB-high ( $\geq 17$  mutations/Mb) and microsatellite instability-high (MSI-H) tumors were more common in young-onset CRC patients compared to older patients. TMB-high status is an emerging biomarker for response to immunotherapy, as it represents a hyper-mutational state that results in a rich expression of neoantigens that can be recognized by the innate immune system and trigger a T-cell response[62,67].

Although the majority of CRCs identified in young patients are not associated with polyposis syndromes or Lynch syndrome, germline mutations in MMR genes still occur at far higher rates in young CRC patients (16%-20%)[1,35] compared to the 3% reported overall rate of HNPCC among all ages[60]. Metastatic tumors with mismatch repair deficiency are candidates for immune checkpoint inhibitors and thus the higher frequency of mutations in MMR genes have important potential therapeutic implications.

Current standard-of-care guidelines include universal microsatellite instability testing for all CRCs; however, using MSI phenotype as a prerequisite for germline testing may not be sensitive enough to detect those with genetic mutations. Current NCCN guidelines recommend genetic evaluation for patients who are diagnosed with CRC prior to age 50[68]. Family history is often used to screen for elevated CRC risk; however, in young-onset CRC patients with germline mutations, only half had a history of CRC in a first-degree relative[35]. Because the majority of young-onset CRC patients do not have an associated hereditary syndrome or germline mutation, traditional algorithms will fail to identify many young patients at risk of developing CRC.

Sporadic young-onset CRC may have a unique molecular profile, in which they have multiple genetic variants displaying variable penetrance[64,69]. The majority of young-onset cancers does not exhibit MSI but are microsatellite stable (MSS). Young-onset MSS tumors demonstrate different manifestations of disease. While late-onset MSS CRCs are predominantly found in the right colon and are less likely to present with synchronous and metachronous tumors, young-onset MSS CRC are left-sided, have a low frequency of other primary neoplasms, and have an important familial component[57]. CpG island methylation (CIMP) silences genes in colon tumors and accounts for 40% of all CRCs[70,71]. CIMP-high tumors are associated with proximal colon location, poor differentiation, MSI, and *BRAF* mutations. Tumors that have *BRAF* V600E alteration and demonstrate *MLH1* promoter hypermethylation are generally sporadic[72]. Young-onset CRC patients have a higher rate of CIMP-low cases and are located in the left colon. However for those patients with Lynch Syndrome who have young-onset CRC, *i.e.*, germline mutations of MSI, a higher proportion will be CIMP-high, compared to those who develop Lynch-syndrome related CRC later in life[70]. Finally, there is a subset of CRCs defined as microsatellite and chromosome stable CRC (MACS), who are characterized by the absence of MSI-high and chromosomal instability (CIN). MACS account for 30% of all sporadic CRC and are identified more frequently in young CRCs[73]. MACS are mostly located in the colon distal to the splenic flexure and rectum, have histologic features associated with poor prognosis, present with metastasis, and have early disease recurrence, and

lower survival rates than patients with MSI or CIN[73]. LINE-1 hypomethylation is a unique feature of young-onset CRC. It is a “surrogate marker for genome-wide hypomethylation” and is associated with increased CIN[74].

### **Genetic testing**

There exist multiple genetic tests that are commercially available. The authors would like to emphasize genetic testing should be performed concurrently with a referral to a genetics counselor or the results should be reviewed with a clinician familiar with the genetic test ordered and its future implications.

### **Referral to fertility specialists**

Young-onset CRC patients often have not completed child-bearing. In order to preserve fertility, referrals should be made to reproductive endocrinology specialists in gynecology and reproductive urologists. Both subspecialties offer cryopreservation of sperm (“sperm freezing”) and ova (“egg freezing”). For females, gynecologists are able to perform ovarian transposition to preserve ovarian function prior to administration of chemoradiation therapy for rectal cancer.

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## **FUTURE DIRECTIONS**

While the recommended age for the first screening colonoscopy has been decreased to age 45 by the American Cancer Society, most other national society guidelines continue to recommend the initial screening colonoscopy at age 50 with consideration for screening colonoscopy for younger adults with “high-risk factors”. A future challenge will be to identify the subset of young patients under age 50 who would benefit from a screening colonoscopy. In a study by Chen, *et al*[20], only one patient in their study sample of patients under age 50 was diagnosed with a familial polyposis. All other patients under age 50 with the diagnosis of CRC were the proband identified by genetic testing in their family. Most patients did not have the recognized risk factors of family history of CRC, personal history of IBD, or hereditary cancer syndrome[20,43]. Thus, there is a need for population-based studies to identify lifestyle and environmental factors associated with young-onset CRC while also investigating the role of traditional risk factors in young-onset CRC. The future challenge lies in identifying the subset population of young patients who would benefit from colorectal screening, while also avoiding societal financial burden.

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## **CONCLUSION**

It has been demonstrated that there is a delay to diagnosis of young patients with CRC, who are diagnosed at more advanced stages of CRC. Clinicians should be hypervigilant of CRC alarm symptoms, family history and genetic syndromes, in order to evaluate, diagnose, and treat CRC in young adults in an efficient manner.

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