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Colon (J Anderson, Section Editor)

Colorectal Cancer in Young Adults

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Abstract

Purpose of review Routine screening for colorectal cancer (CRC) in adults > 50 years of age has led to overall reductions in CRC incidence and CRC-related mortality. Yet CRC incidence among young adults age < 50 continues to increase without a clear explanation. This review examines the changing epidemiology of CRC and emerging evidence regarding the influence of genetic and lifestyle factors on risk for colorectal neoplasia.

Recent findings Young-onset CRC (yCRC), defined as CRC diagnosed in individuals younger than age 50, is a heterogeneous disease. Approximately, one in every five individuals affected with yCRC carries a pathogenic germline variant in genes associated with predisposition to cancer. However, most have no clinically identifiable risk factors. Analyses of birth cohorts estimate CRC risk among millennials to be 2–4 times higher than their grandparents', suggesting that changes in health behaviors and environmental factors are having an impact on CRC risk. Young individuals with CRC tend to be diagnosed at later stages and often present with metastatic disease. yCRC tumors arise predominantly in the distal colon and are more likely than older-onset tumors to exhibit microsatellite and chromosome stable (MACS) phenotypes. Although yCRC patients are more likely than their older counterparts to be treated with multimodality chemotherapy regimens, more aggressive treatments have not yielded measurable survival gains. Since one in ten new CRC diagnoses involve individuals age < 50, recent guidelines have proposed lowering the age for average risk CRC screening from 50 to 45; however, further studies are needed to evaluate testing strategies based on individuals' age and risk.

Summary Significant shifts in CRC epidemiology and diversity of tumor phenotypes support genetic and environmental factors as modifiers of cancer risk. Emerging data correlating tumor molecular features with outcomes justify further investigation into mechanisms of carcinogenesis to elucidate how specific factors (inherited and/or acquired) might stimulate young-onset colorectal neoplasia.

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the USA [1]. Implementation of CRC screening in the mid-1990s has significantly decreased CRC incidence and mortality in individuals over the age of 50 [1–3]. Paradoxically, a measurable increase in CRC incidence among individuals under the age of 50 years has been observed, which can be traced back to 1990 [2, 4]. While a number of possible explanations for this trend have been suggested, a clear causative factor has yet to be elucidated. Since most individuals affected with yCRC would otherwise be categorized as average risk, some groups have recommended that screening be expanded to decrease the burden of yCRC. Understanding the reasons underlying the recent increase in yCRC is necessary to guide the development of effective interventions. Here, we review the changing epidemiology of yCRC, tumor molecular features, and potential explanations for the increasing incidence of colorectal neoplasia in young individuals, which impact approaches to yCRC treatment and prevention.

Epidemiology

Since the implementation of routine screening for CRC in the 1990s, there have been significant and persistent overall decreases in both CRC incidence and mortality [1–3, 4, 5•, 6, 7]. Unfortunately, this trend pertains only to individuals over the age of 50, while CRC incidence among young individuals age < 50 continues to rise with annual increases approaching 1.4% for colon cancer and 2.4% in rectal cancer as measured from 2005 to 2014 [1]. The changing epidemiology of CRC is well illustrated by several studies analyzing data from the US Surveillance, Epidemiology, and End Results (SEER) program demonstrating that CRC incidence increased by 1.4% per year among individuals aged < 50 while decreasing by 3.1% per year among those > 50 years old [3, 5, 8, 9•, 10, 11]. Along with the estimated 51% relative increase in CRC incidence among individuals age < 50 [12••], there has also been an increase in yCRC mortality, up 13% from 2000 to 2014, which stands in stark contrast to the 34% decrease in CRC mortality observed among individuals age > 50 years [3]. Interestingly, the sharpest rise in CRC mortality is seen among young non-Hispanic White individuals [12••]. Although overall CRC mortality rates have declined over time, racial disparities persist with Blacks with yCRC experiencing worse outcomes compared to non-Hispanic Whites and Hispanics at every disease stage, but most pronounced among those with stage II colon cancer and stage III rectal cancer [13].

Approximately, 10% of incident CRCs are now diagnosed in individuals aged < 50 [3] with the largest burden occurring in those aged 40–49, accounting for 75% of the yCRC cases [9•, 14]. Comparison of CRC incidence patterns over time demonstrates a dramatic increase from 8.3 to 11.8 per 100,000 from 1990 to 2014, with age-specific incidence rates increasing in successive birth cohorts, supporting hypotheses that changes in lifestyle (e.g., diet, patterns of antibiotic use) are having an impact on CRC risk [4].

Clinical features of young-onset CRC

CRCs often present differently in young adults. Multiple studies have noted that a higher proportion of yCRCs arise in the sigmoid colon and rectum [3, 7, 15–18]. When compared to their older counterparts, young CRC patients tend to

have a higher rate of red flag symptoms, such as rectal bleeding, obstruction, or abdominal pain [16, 19]. Failure to consider CRC as a potential diagnosis often delays the diagnostic process, with patients under the age of 50 years having a 1.4-fold increase in time to diagnosis than their older counterparts [20]. Consequently, a higher proportion of yCRCs present at a later stage [21, 22]. One multicenter retrospective study comparing CRC in patients 18–44 years and > 44 years found 61.2 and 44.5% had metastatic disease at diagnosis [23•]. It has been suggested that tumors in patients under 40 years old seem to have more aggressive histologic subtypes compared to their older counterparts, with 13 versus 1% of samples showing signet ring histology, 29 versus 11% showing perineural invasion, and 22 versus 6% showing venous invasion [24].

Molecular subtypes of CRC

Although data on molecular characteristics of yCRC tumors are limited, reports suggest that there are underlying differences in the biology of older onset vs yCRC.

CRCs, as a whole, encompass a heterogenous group of cancers with the majority of CRCs falling into a limited number of molecular subtypes. While a comprehensive review of the molecular subtypes of CRC is not provided here, it can be referenced elsewhere [25–27]. Briefly, of the three main molecular subtypes, the majority of CRCs exhibit the chromosomal instability (CIN) subtype, which typically displays chromosomal aneuploidy and a stepwise accumulation of mutations in specific genes including *APC*, *KRAS*, *TP53*, and *BRAF*. The microsatellite instability (MIN) subtype is characterized by microsatellite instability (MSI) due to loss of DNA mismatch repair (MMR) and can arise sporadically or be associated with germline alterations in MMR genes (Lynch syndrome) resulting in hypermutated tumors. Finally, the CpG island methylator phenotype (CIMP) displays widespread methylation changes resulting in epigenetic silencing. These subtypes can additionally display some overlap and are not mutually exclusive, with a minority of CRCs exhibiting both microsatellite and chromosome stability (MACS).

Interestingly, preliminary studies suggest differences in the proportion of molecular tumor subtypes between older-onset and yCRC. Among older-onset CRCs, a majority of cases exhibit CIN (51%), while MACS (34%) and MSI (13%) account for only a minority. However, among yCRCs, most exhibit MACS (45%) and MSI (21%) phenotypes, with lower proportions of CIN subtypes (32%) [28]. The higher prevalence of MSI in the yCRC group has been attributed to the increased prevalence of Lynch syndrome, the most common of the hereditary colorectal cancer syndromes.

Although data are limited, the MACS subtype which appears to be more common in the yCRC group and also appears to be associated with worse disease-free survival [28, 29]. LINE-1 hypomethylation, a surrogate marker for global hypomethylation, has also been found to be more prevalent in yCRCs and is associated with poorer prognosis [30].

The differences in molecular subtypes in yCRC come with significant clinical implications. For example, CRCs exhibiting MMR deficiency typically have poor response to fluorouracil-based adjuvant chemotherapy [31]. Interestingly, however, patients with MMR-deficient tumors tend to exhibit better overall survival, attributed to the more immunogenic nature of MIN subtype [32].

Although assessment of tumor MSI phenotype is recommended for all CRCs with implications for treatment, prognosis, and for diagnosing Lynch syndrome, in clinical practice, MSI testing is performed in only a minority of yCRC patients [10].

Treatment of CRC in young patients

Evidence regarding outcomes and effectiveness of specific treatment regimens in yCRC remains scarce. Currently, no evidence-based age-specific treatment regimens exist for CRC, though some recent reports do suggest differences in treatment outcomes between yCRC and older-onset CRC.

Several studies have reported that young patients are more likely to be treated with adjuvant chemotherapy regardless of the presence of distant metastases [33]. Kneuertz et al. investigated a nationwide cohort of CRC cases diagnosed age 18–49 years and found that compared to those age 65–75 years, younger patients were more likely to receive systemic chemotherapy and these more intensive regimens were not associated with increased survival in stage I or stage II cancers and offered only marginal benefit in stage III or stage IV diseases [34•]. Similarly, Manjelievskaia et al. investigated the differences in chemotherapy use and outcomes in colon cancer patients in ages 18–49 (young), 50–64 (middle-aged), and 65–75 (older) and found that young and middle-aged patients were more likely to receive adjuvant chemotherapy but did not show a significant improvement in survival compared to their older counterparts [35••]. Based on these retrospective observational studies, it is unclear whether current clinical practice tends toward overtreatment of yCRC patients compared to their older counterparts (with marginal benefit) or whether the underlying biology of yCRCs may be more aggressive, requiring more aggressive treatment to match outcomes. Currently, no guidelines recommend modifying CRC treatments based on young age and additional prospective studies and randomized clinical trials are needed to determine the optimal treatment regiments for younger patients.

Future directions regarding specific treatment options are currently being explored. Recent observations also highlight a significant difference in tumor mutation rates involved in histone methylation and demethylation which play an important role in CRC pathogenesis [36, 37]. With a better understanding of the molecular differences between yCRC and their older counterparts, it may be possible to exploit specific molecular alterations for the treatment of yCRC.

The role of genetic predisposition syndromes

It is important to consider the possibility of an underlying genetic predisposition to cancer in every individual affected with yCRC. Next-generation sequencing multigene panel genetic tests identify pathogenic germline variants in 16–20% of yCRC cases, involving genes associated with high and moderate penetrance cancer syndromes (Table 1) [38, 41••]. Lynch syndrome and familial adenomatous polyposis are the most prevalent syndromes, associated with early onset of colorectal neoplasia requiring colonoscopy beginning at age 20–25 and 10–12, respectively [39]. However, the variability in clinical presentations and potential for phenotypic overlap justifies the recommendation for genetic testing using a multigene panel for all individuals with yCRC [40].

Table 1. Genes implicated in yCRC

Genes	Syndrome	Common associated cancers
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome DNA mismatch repair (MMR)	Colorectal Endometrial Gastric Pancreatic Small bowel
APC	Familial adenomatous polyposis (FAP)	Colorectal Duodenal/ampullary Thyroid Pancreatic Desmoid tumors
MUTYH	MUTYH-associated polyposis (MAP)	Colorectal Thyroid
BMPR1A *SMAD4*	Juvenile polyposis syndrome	Colorectal Gastric
STK11	Peutz Jeghers syndrome	Breast Gastric Colorectal Pancreatic Sex cord
TP53	Li Fraumeni syndrome	Breast Gastric Colorectal Brain Sarcoma Lung
PTEN	Cowden/PTEN hamartoma tumor syndrome	Breast Endometrial Thyroid Colorectal
POLE *POLD1*	Polymerase-proofreading-associated polyposis (PPAP)	Colorectal Endometrial
GREM1	Hereditary mixed polyposis syndrome (HMPS)	Colorectal
BRCA1 *BRCA2* *PALB2*	Hereditary breast ovarian cancer syndrome	Breast Ovarian Pancreatic (± gastrointestinal)
CHEK2 *ATM*	Moderate penetrance cancer risks	Breast Thyroid Pancreatic (± gastrointestinal)

Whereas earlier reports suggested genetic testing would be low yield in the absence of family history of CRC, genetic testing uncovers genetic diagnoses in approximately one in every five yCRC cases, with only half of germline

mutation carriers reporting a family history of CRC [41••]. Making the diagnosis of a hereditary cancer syndrome can have an impact on surgical approaches (e.g., subtotal colectomy instead of segmental resection), selection of chemotherapy regimen, colonoscopy surveillance intervals, and surveillance for extracolonic cancers [39]. Furthermore, predictive genetic testing can be used to identify at-risk relatives who would benefit from early colonoscopy.

Possible explanations for the rising incidence of yCRC

The underlying cause(s) for the rise in incidence of yCRC remains elusive. A number of theories have been put forth which invoke both genetic and lifestyle factors. Although germline genetic alterations can be implicated in one in five individuals with yCRC, hereditary syndromes account for only a minority of cases. Since the prevalence of pathogenic variants in a population does not change significantly over time, genetic factors alone would not explain the recent increase in CRC incidence [16, 42]. Potential interactions between genetic risk alleles and comorbidities such as obesity [43, 44], diabetes [45], and lifestyle factors such as consumption of processed meat, alcohol, and tobacco use [42, 46, 47] are being explored through risk modeling [48]. Metabolic changes in insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2) have been associated with pro-carcinogenic effects [49]. A recent study investigated risk factors of CRC in young adults from ages 20–39 and found metabolic syndrome (obesity, elevated blood pressure, abdominal obesity), smoking status, and alcohol intake were independently associated with a higher risk of CRC, while tobacco use and alcohol intake were not significant risk factors in the very young age group (20–29) [50]. Birth cohort analyses of CRC incidence data suggest rates of yCRC had been decreasing just prior to the recent sharp increases with an inflection point in the mid-1990s, suggesting that recent changes in exposures that might alter the gastrointestinal microbiome (e.g., diet, antibiotic use) warrant further investigation [4].

Additional studies linking health behaviors with disease phenotypes will be important for assessing the potential influence of modifiable risk factors on CRC risk and developing novel approaches to CRC treatment and prevention.

Strategies for primary and secondary CRC prevention in young adults

In this review, we define yCRC as cases diagnosed at age < 50. While most reports in the literature use a similar definition, this age cutoff is artificial, based primarily on the current age at which it has been recommended for average-risk adults to begin CRC screening [51, 52]. Individuals who are above average risk for CRC (due to family history of colorectal neoplasia or personal history of inflammatory bowel disease) are recommended to commence CRC screening earlier [51]. The American College of Gastroenterology stood out from peer organizations by recommending earlier screening for Black individuals starting at age 45 [53] based on observed racial disparities in CRC incidence and outcomes [9•, 10].

Current CRC screening recommendations were based on CRC incidence data from 1975 to 1979 and do not account for the more recent

increases in yCRC incidence. A recent modeling analysis adjusted CRC screening models using updated incidence data [54••] concluded that in order to maintain a similar burden to benefit ratio as previous recommendations, average risk screening should start at age 45 rather than 50. Based on this, the American Cancer Society issued an updated guideline with qualified recommendation to lower the age for average-risk screening to 45 [12••]. This change has generated considerable debate given the paucity of data about the effectiveness of the various CRC screening tests (endoscopic vs stool-based) in younger patients [55]. A recent analysis concluded that screening individuals age 45–49 years would prevent 900 CRC-related deaths at a cost of $5.5 billion [56].

There is a clear need for more effective ways to stratify individuals' CRC risk. However, a significant proportion of yCRC cases could be prevented by identifying individuals eligible for earlier screening by current guidelines. Clinicians should review family history of cancer that includes all diagnoses in first and second-degree relatives to determine whether a patient's risk for colorectal neoplasia is average, moderate, or high. In addition, the use of genetic risk models (e.g., PREMM5 www.premm.dfci.harvard.edu) can be helpful for identifying individuals who meet criteria for genetic testing [57].

Conclusions

Incidence of CRC has been increasing among individuals age < 50 for unclear reasons. Existing data suggest that yCRC patients represent a heterogeneous group. Young-onset tumors differ from older-onset CRCs in their clinical characteristics, pathologic features, molecular profiles, and potentially, response to treatment. Additional studies are needed to elucidate the etiology of the rising incidence of yCRC in order to determine how best to implement screening based on risk and target treatments to the molecular mechanisms which drive colorectal neoplasia in young adults.

Compliance with Ethical Standards

Conflict of Interest
Anand Venugopal declares that he has no conflict of interest.
Elena Stoffel declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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- •• Of major importance

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