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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Colon Cancer in Young Adults: Trends and Their Implications

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Abstract

Purpose of Review The recent rise of young individuals under age 50 with colorectal cancer (CRC) is a startling trend in need of greater focus and research. The etiology of young-onset CRC is unexplained as efforts to blame obesity or diabetes as causative factors are simplistic and inadequate.

Recent Findings We describe the epidemiologic shifts of CRC incidence and mortality across age groups as well as the differences in clinicopathologic, molecular, treatment, and survival characteristics between young and older patients. Novel studies of the microbiome may elucidate bacterial causes of CRC carcinogenesis in younger individuals. Moving up the colonoscopy screening to age 45 in normal-risk individuals should prove beneficial in detecting more patients with early-onset CRC.

Summary We favor the development of risk-adaptive screening decision algorithms and flexible sigmoidoscopy screening at age 40 given the predilection for left-sided primaries in this age group. More awareness and attention to young-onset CRC will be critical to improve outcomes in this patient population.

Keywords Young-onset · Colon cancer · Rectal cancer · Colorectal cancer screening · Molecular profiling

Introduction

Colorectal cancer (CRC) is the second-leading cause of cancer-related deaths in the USA [1]. An estimated 140,250 people will be diagnosed with CRC in 2018, and an estimated 50,630 will die from the disease [1]. Overall, the incidence and death rates for CRC are on the decline [2•]. However, this trend is not observed across all subgroups. Since the late 1980s, colonoscopic screening has benefited older individuals and helped lead to improved outcomes. While CRC incidence and death rates have fallen for individuals older than 50 years, the opposite is true for individuals younger than 50 years [2•]. Since the year 2000, the incidence and death rates of CRC in younger individuals have been rising, and this finding has not been adequately explained. The American Cancer Society recently recommended lowering the colonoscopy screening age for normal-risk individuals from 50 to 45 years; however, this recommendation will not benefit those normal-risk patients with CRC under age 45 and does not address efforts to understand why colon cancer is becoming more prevalent in younger individuals [3•]. In this review, we explore etiologies behind the rise in incidence and mortality in young patients with CRC.

Epidemiology

CRC is still predominately a cancer of older individuals. The median age at diagnosis is 67, and only 21.2% of patients are diagnosed with CRC before age 55 [4]. With the advent of widespread colonoscopic screening, the incidence and death rates of CRC in patients older than 65 years have declined dramatically since the mid-1980s (Fig. 1) [5]. Colonoscopic screening not only detects CRC at an earlier stage, but it also facilitates the removal of pre-malignant polyps prior to formation of invasive cancer. Over the last 20 years or so, the incidence rate of CRC in patients younger than 50 years has risen quite dramatically and the death rate has risen since the year 2000 (Fig. 1). For gastrointestinal medical oncologists who treat these patients, this trend is impossible to miss as more and more young CRC patients appear in our clinics.

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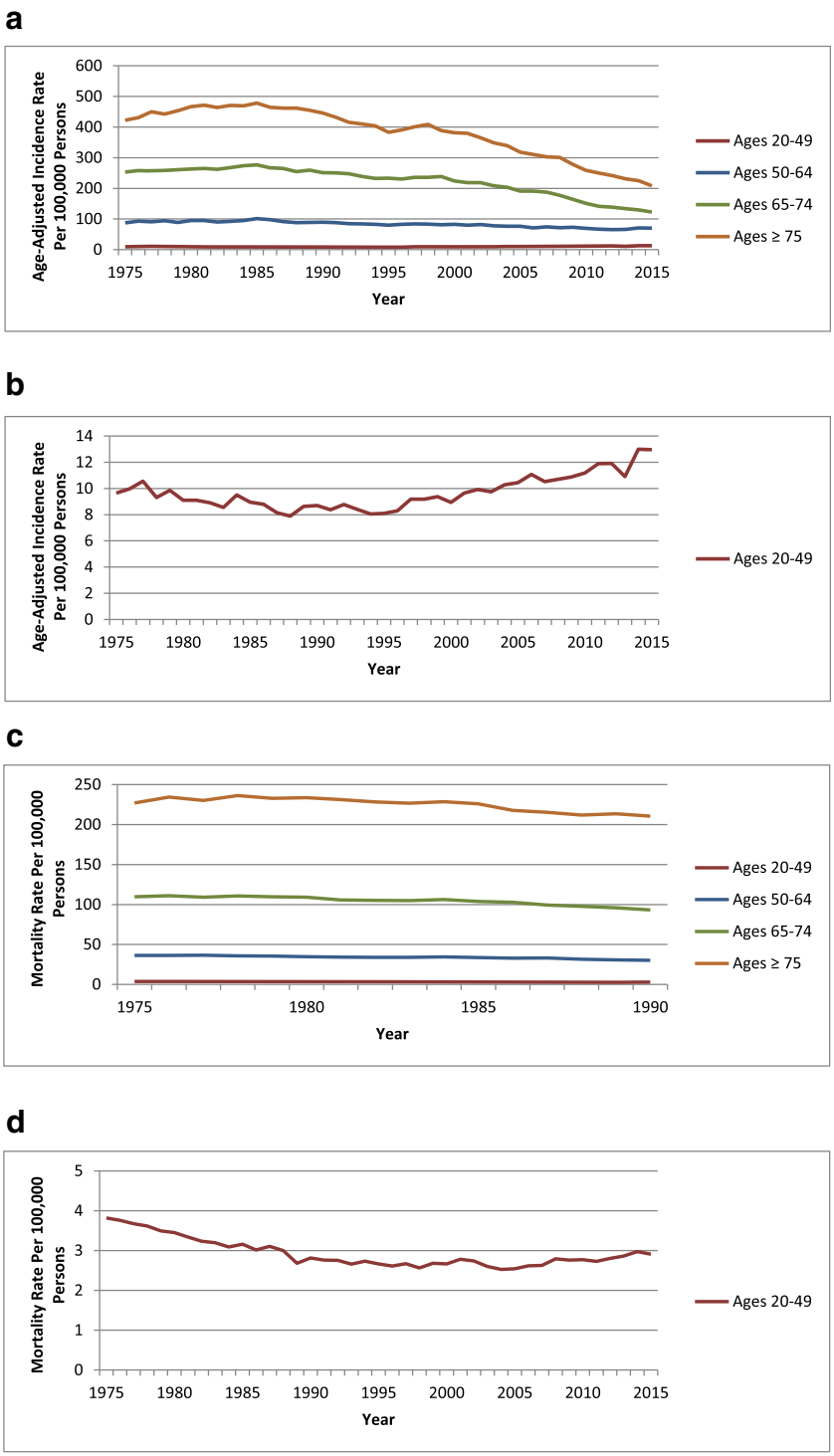

Fig. 1 Trends in CRC incidence in all age groups above age 20 (**a**), ages 20–49 (**b**), and trends in CRC mortality in all age groups above age 20 (**c**) and ages 20–49 (**d**) [5]

While the rise of CRC in the young persists across racial and ethnic groups in the USA, the rate of change in incidence rates varies with ethnicity. Between 2000 and 2013, CRC incidence in patients under 50 years of age increased with annual changes of 2.5% in American Indian/Alaskan Natives, 2.3% in non-Hispanic whites, 1.0% in non-Hispanic blacks, and only 0.2% in Asian/Pacific Islanders [2•]. The higher CRC incidence rates in Alaskan Natives are historically thought to stem from high-fat diets, obesity, diabetes, vitamin D deficiency, and smoking, but the recent rise in the non-Hispanic white population is not as well explained [6]. While the incidence of CRC is almost 50% greater in men than women in the 55–74-years age group, CRC incidence is very similar between men and women diagnosed before age 40 [2•].

Younger patients with CRC tend to have tumors more frequently arising from the left side of the colon (descending and

sigmoid) and rectum, whereas older patients with CRC tend to have right-sided tumors (cecum, ascending, and proximal transverse colon). The left and right side of an individual's colon result from different embryologic structures (the hindgut and midgut, respectively) with different blood supplies. Recent studies have shown underlying differences in left-sided and right-sided CRCs. In particular, right-sided tumors have higher rates of *BRAF* mutations and microsatellite instability (MSI) than left-sided tumors [7]. Rather than a dichotomous split between left and right, tumor mutational frequencies vary throughout the colon in a continuum of molecular alterations. Regions within the left and right sides also carry unique molecular features, such as the rectosigmoid and transverse colon [8]. Tumor sidedness is important clinically in metastatic CRC as patients with right-sided tumors have overall inferior survival and do not benefit from therapy targeting the epidermal growth factor receptor (EGFR) even if their tumors are *RAS* wild-type, while those with left-sided *RAS* wild-type tumors experience a significant survival benefit with EGFR-directed therapy [9–12].

As one would expect, the recent wave of young patients with CRC mostly involves tumors in the left side of the colon and rectum. Why do younger patients more often develop left-sided CRC? Some hypothesize that estrogen has a protective effect on the development of right-sided CRC, and as estrogen levels decline with age, CRC becomes more prevalent in the right colon [13]. In particular, higher estrogen exposure protects women against MSI-high tumors that more often occur in the right colon [14]. In a similar pattern, DNA methylation within colon cancer epithelial cells increases with age, resulting in a higher rate of CpG island methylator phenotype high (CIMP-high) CRCs in older patients, which are almost exclusively right-sided [15, 16]. Thus, right-sided CRCs are more common in older patients in part due to a greater rate of MSI-high and CIMP-high cancers.

Hereditary CRCs

Approximately 30% of patients with CRC have a family history of CRC (familial CRC), but only around 5% of patients with CRC have an identifiable hereditary CRC syndrome [17]. However, the rates of hereditary CRC syndromes are higher in younger patients. Pearlman and colleagues studied 450 patients with CRC younger than 50 years of age and found that 16% of patients had a germline mutation in at least one of 25 cancer susceptibility genes (Fig. 2) [18•]. Interestingly, 26% of patients found to have a germline mutation did not have a known first-degree relative with a history of cancer, and 33% did not meet the established testing criteria for their genetic syndrome. Patients with germline mutations tended to be closer to 50 years of age, with a median age of 41 years and 65% older than 40 years. Another study by Mork and colleagues found that 35% of 193 patients with CRC diagnosed before age 35 had a hereditary CRC syndrome [19]. In this study, only 19% of patients with hereditary syndromes had a family history of CRC. Therefore, it is imperative to offer genetic counseling to CRC patients under age 50, and this recommendation is supported by the National Comprehensive Cancer Network (NCCN) [20].

The most common CRC syndrome is hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (LS). This disorder arises from an inherited autosomal dominant mutation in one of the mismatch repair proteins (*MLH1*, MSH2, *MSH6*, *PMS2*, or *EPCAM*) and is associated with CRC, endometrial, small bowel, and ureteral cancers [21]. Individuals with LS have an 80% lifetime chance of developing CRC. Women with LS should undergo endometrial and ovarian cancer screening. Traditionally, the Amsterdam II criteria were used to screen individuals for LS (≥ 3 relatives with a LS-related cancer, ≥ 2 generations affected, ≥ 1 relative diagnosed before age 50, and familial adenomatous polyposis [FAP] excluded) [22]. The Revised Bethesda Guidelines offer a more sensitive screening test (CRC in a patient under 50 years old, synchronous or metachronous LS-related cancers, MSI-high histology and under age 60 years old, ≥ 1 first-degree relative with CRC and a LS-related cancer with at least one diagnosed before age 50, or ≥ 2 first-degree relatives with a LS-related cancer at any age) [23]. However, these screening guidelines miss a substantial number of patients with hereditary CRC without a family history, as described in the work by Pearlman and Mork [18•, 19]. Therefore, we favor genetic counseling for all patients with CRC diagnosed before age 50.

The other common hereditary CRC syndrome is FAP. FAP results from an autosomal dominant inherited mutation in the *APC* gene and manifests itself as 100s to 1000s of colonic polyps. Unlike LS, patients with FAP have a 100% chance of developing CRC by age 45; therefore, the definitive treatment is a total proctocolectomy. FAP is also associated with Turcot syndrome (central nervous system tumors) and Gardner syndrome (desmoids, lipomas, osteomas, and fibromas) [24, 25]. Other polyposis syndromes include attenuated FAP (other *APC* mutations, 80% lifetime risk of CRC, fewer polyps), *MUTYH*-associated polyposis (autosomal recessive), Peutz–Jeghers syndrome (*STK11* autosomal dominant mutations, hamartomatous polyps), juvenile polyposis syndrome (*SMAD4* mutations, hamartomas), and polymerase proofreading-associated polyposis (PPAP, *POLE* or *POLD1* autosomal dominant mutations) [26–30].

Familial CRCs

Having a first-degree relative with CRC increases one's risk by 1.72- to 2.25-fold, and if the relative was 45 years or younger at diagnosis, the relative risk increases to 3.87–5.37 [31,

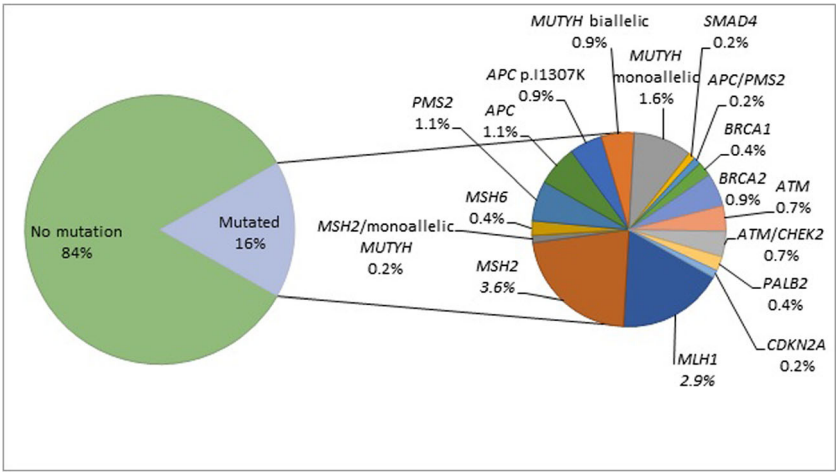

Fig. 2 Germline mutations identified in patients diagnosed with CRC younger than 50 years of age. Data from Pearlman et al. [18•], $N = 450$

32]. If more than one relative has CRC, the relative risk increases to 2.75–4.25. Interestingly, there is only a minimally increased risk of CRC from a positive family history after age 60 [32]. Colonoscopy screening should commence 10 years before the age of diagnosis of the youngest affected relative or age 40, whichever is earlier [33].

Clinicopathologic Characteristics

Younger patients tend to have more aggressive tumor histologies and advanced disease. In a study of 6775 patients with stage I–III CRC, patients aged 40 years or younger were more likely to have lymphovascular invasion (35% vs. 27%; $P = 0.005$), T3/T4 tumors (88% vs. 79%; $P = 0.005$), and stage III disease (58% vs. 41%; $P < 0.001$) than patients older than 60 years [34]. In another large study of 369,796 patients with CRC diagnosed between 2000 and 2011, patients diagnosed between the ages of 20 and 49 years had higher rates of signet ring cell histology (1.9% vs. 0.9%; $P < 0.001$) and metastatic disease at diagnosis (24.4% vs. 18.8%) than patients aged 50 years and older [35]. Mucinous histology is a well-known negative prognostic factor and is more commonly seen in the younger CRC population [36]. Li and colleagues studied 69,835 patients in the SEER database and found that patients aged 40 years and younger had tumors with higher grade ($P < 0.001$), mucinous and signet-ring histologies ($P < 0.001$), stage ($P < 0.001$), and positive lymph nodes ($P < 0.001$) than patients over 40 years of age [37]. Thus, younger patients are more likely to have higher stage disease and tumors with more aggressive histologic subtypes.

Molecular Characteristics

Genetic drivers of CRC in young and older patient populations are remarkably similar. In a study comparing left-sided tumors in 1126 patients with CRC diagnosed at age 45 and younger or age 65 and older, significant differences were seen in the rates of mutations in *MSH6* (4.8 vs. 1.2%; $P = 0.005$), *MSH2* (2.7% vs. 0%; $P = 0.004$), *POLE* (1.6% vs. 0%; $P = 0.008$), *NF1* (5.9% vs. 0.5%; $P < 0.001$), *SMAD4* (14.3% vs. 8.3%; $P = 0.024$), and *BRCA2* (3.7% vs. 0.5%) [38]. Thus, there were no dramatic differences in mutational profiles between the groups, and it is not surprising that LS genes (*MSH2* and *MSH6*) were more commonly mutated in the younger group where MSI-H tumors seen in LS were also more common (8.1% vs. 1.9%; $P = 0.009$). More interesting is the finding that higher tumor mutational burden (≥ 17 mutations per megabase) was seen more frequently in tumors from younger patients (9.7% vs. 2.8%; $P < 0.001$), suggesting that younger CRC patients may be more likely to benefit from immunotherapy using checkpoint inhibition [39]. While we do not recommend routine next-generation sequencing of all tumors in young CRC patients outside the metastatic setting, we do routinely test tumors of all stages for MSI-H in order to potentially identify patients with LS, decreased benefit from adjuvant chemotherapy in stage II disease, and sensitivity to immune checkpoint blockade in stage IV disease [40–43].

Treatment

Multiple studies have demonstrated that young patients with CRC receive more aggressive therapy than older patients do in both the adjuvant and metastatic settings. Patients younger than 50 years of age more frequently receive adjuvant chemotherapy and multi-agent adjuvant chemotherapy. This treatment approach provides minimal survival benefits for patients with stage III–IV disease and no benefit for patients with stage II disease [44]. Younger patients are also more likely to undergo resection of the primary tumor in the setting of metastatic disease than their older counterparts (70.8% vs. 66.6%; $P < 0.001$) [45]. Therefore, serious consideration must be

made regarding the overtreatment of young CRC patients with adjuvant chemotherapy, especially for those with stage I–II disease.

Survival

Despite presenting with generally more aggressive and advanced disease than their older counterparts, young patients with CRC tend to have superior survival outcomes [34]. Interestingly, stage II right-sided CRC in young patients (20–39 years of age) was associated with improved survival over left-sided CRC, whereas stage III right-sided CRC in patients aged 40–49 years was associated with inferior survival [46]. In a study of 498 CRC patients, those diagnosed before age 45 had inferior progression-free survival on first-line therapy for noncurative disease compared with older patients (hazard ratio [HR] 1.96, 95% confidence interval [CI] 1.04–3.68), but overall survival was similar (HR 1.53, 95% CI 0.91–2.58) [47]. Using SEER data, Li and colleagues demonstrated that CRC patients aged 40 years and younger had superior 5-year CRC-specific survival rates (78.6% vs. 75.3%; $P < 0.001$) than their counterparts aged over 40 years, despite more advanced stage and aggressive histologies in the younger group [37].

Microbiome

The prevailing explanations for the rise in young patients with CRC are not satisfactory. The epidemics of obesity and diabetes are frequent scapegoats, but these conditions do not explain the etiology of the vast majority of young patients with CRC. The colon microbiome composition reflects an interplay between the host immune system, environment (including diet), and genetics. We hypothesize that alterations within the stool microbiome may plan a significant role in the pathogenesis of CRC in younger patients. Bacterial composition changes both spatially, depending on location within the colon, and chronologically as individuals age [48, 49]. Specific culprit bacteria have been identified as instigators of CRC carcinogenesis, including *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Streptococcus gallolyticus* (formerly *Streptococcus bovis*), and certain strains of *Escherichia coli* [50]. In addition, bacterial biofilms appear to play a distinct role in the pathogenesis of right-sided CRC, especially in FAP patients [50, 51]. Studies in older patients with CRC have shown that *Fusobacterium nucleatum* can play a significant role in CRC carcinogenesis, especially in right-sided tumors [49]. *Fusobacterium nucleatum* travels as CRC metastasizes in mice, and murine tumors with *Fusobacterium nucleatum* respond to the antibiotic metronidazole [52]. These findings suggest potential future studies evaluating antibiotics, probiotics, and even stool transplantation to target CRC. We are actively investigating differences in intratumoral and stool bacterial composition in young and older CRC patients using 16S ribosomal RNA sequencing, aiming to elucidate novel signals of specific carcinogenic bacteria in younger patients.

Screening Recommendations

As mentioned previously, the American Cancer Society has lowered their colonoscopy screening recommendation from 50 to 45 years of age in patients at normal risk for developing CRC [3•]. Others have posited using screening flexible sigmoidoscopy starting at age 40, given the tendency for young individuals to develop left-sided primary tumors of the sigmoid colon or rectum [53]. It is imperative to identify patients at above-normal risk, which includes individuals with a personal history of CRC, inflammatory bowel disease (IBD), polyps, abdominal radiation, or a family history of CRC or a hereditary CRC syndrome (e.g., HNPCC or FAP). Individuals with above-average risk of CRC warrant screening colonoscopies at the following times in their lives, whichever comes first: at age 40, 10 years before their youngest family member's diagnosis with CRC, or 10 years following the diagnosis of IBD [33]. Other risk calculators are in development that include lifestyle and environmental factors as well as genetic analyses using CRC-associated single-nucleotide polymorphisms (SNPs) [54]. We hope that future risk-adapted screening methodologies will be able to selectively screen younger individuals at high risk of CRC while sparing other relatively young but lower risk individuals who could receive traditional screening colonoscopies starting at age 50. In the future, a better understanding of the stool microbiome in CRC patients may enable us to select young patients suitable for early colonoscopic screening based on a high-risk bacterial signature from a stool sample.

Conclusions

We do not yet know the etiology of the recent rise of CRC incidence and mortality in young patients, although we hope that insights into intratumoral microbiome may offer at least a partial explanation. Management of young patients with CRC is complex and there is no satisfactory one-size-fits-all approach. Despite having more aggressive histologies and advanced stages, survival outcomes from CRC are still favorable in the younger population. While earlier colonoscopies starting at age 45 should detect a larger number of younger patients with CRC, we favor the development of novel risk calculators utilizing lifestyle, environmental, genetic, and (eventually) microbiome factors for those at traditionally normal risk in order to select individuals likely to benefit from

early colonoscopies. More research is clearly needed regarding the etiology and treatment of CRC in younger patients.

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Compliance with Ethical Standards

Conflict of Interest Benjamin A. Weinberg has received research funding from Novartis and has received compensation from both Eli Lilly (speakers bureau) and Caris Life Sciences (travel reimbursement). John L. Marshall declares that he has no conflict of interest.

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