Colorectal Cancer in the Young: Epidemiology, Prevention, Management

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overview

Colorectal cancer (CRC) incidence rates in the United States overall have declined since the mid-1980s because of changing patterns in risk factors (e.g., decreased smoking) and increases in screening. However, this progress is increasingly confined to older adults. CRC occurrence has been on the rise in patients younger than age 50, often referred to as early-onset disease, since the mid-1990s. Young patients are more often diagnosed at an advanced stage and with rectal disease than their older counterparts, and they have numerous other unique challenges across the cancer management continuum. For example, young patients are less likely than older patients to have a usual source of health care; often need a more complex treatment protocol to preserve fertility and sexual function; are at higher risk of long-term and late effects, including subsequent primary malignancies; and more often suffer medical financial hardship. Diagnosis is often delayed because of provider- and patient-related factors, and clinicians must have a high index of suspicion if young patients present with rectal bleeding or changes in bowel habits. Educating primary care providers and the larger population on the increasing incidence and characteristic symptoms is paramount. Morbidity can further be averted by increasing awareness of the criteria for early screening, which include a family history of CRC or polyps and a genetic predisposition.

CHANGING EPIDEMIOLOGY

Rising incidence of early-onset CRC (EO-CRC) was first noted at the population level in 2003[1] but did not begin to gain traction as a public health concern for another decade after publication of a second report.[2] In the years since, epidemiologic studies have provided clues for what might be causing the trends. For example, incidence patterns are consistent in men and women, implicating exposures that are not sex-specific but vary by anatomic subsite, stage at diagnosis, race and ethnicity, and geographic area of residence. Inclines are steepest for advanced-stage disease, for tumors in the distal colon and rectum, and among non-Hispanic whites.[2-7] A recent study based on cancer registry data from 47 states found that incidence is increasing among non-Hispanic whites in most states, with the most rapid pace in the West.[6] From 1995 to 2015, for example, the CRC incidence rate in people younger than age 50 increased by 57% in Colorado and by 73% in Washington State. However, contemporary incidence rates remained generally highest in the South and lowest in the West. The unique increase among young people is also occurring outside the United States in many high-income countries, including Australia, Canada, Germany, and the United Kingdom.[8-10]

In the United States and elsewhere, the CRC incidence pattern is characterized by a strong birth cohort effect.[5,8,11] A birth cohort effect occurs when age-specific incidence rates vary by generation because of changes in exposure that influence disease risk, in contrast to period effects, in which incidence varies at the same point in time for all age groups. In the United States, people born in the 1950s have the lowest CRC incidence, and the risk of disease since has increased with each subsequent generation after declining in the first half of the 20th century.[5] The phenomenon is clearly visible when temporal trends are stratified by granular age groups, because the elevated risk of disease travels with particular birth cohorts as they advance in age. Among young adults, for example, previously declining colon cancer incidence began increasing in the mid-1980s among people age 20 to 29 but not until the late-1980s in ages 30 to 39 and the mid-1990s in ages 40 to 54.[5] During the past decade, an accompanying increase in mortality has emerged, with CRC death rates increasing by more than 1% per year since 2004 among adults younger than age 55 after previously declining trends.[12,13] Rates have recently begun to tick up in people age 50 to 64, for reasons that are unknown.[12] A consequence of these oppositional trends is an increasingly younger patient population; the median age at CRC diagnosis has decreased from age 72 in the early 2000s to age 66 today (Fig. 1).[14]

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PRACTICAL APPLICATIONS

- The rate of early-onset CRC (< 50 years at diagnosis) has been increasing for 2 decades for unknown reasons.
- Screening for CRC in average-risk patients (no family history or predisposing conditions) is recommended by the American Cancer Society to begin at age 45.
- Patients present with characteristic symptoms of abdominal pain, rectal bleeding, and changes in bowel habits, but diagnosis often is delayed.
- Currently, patients with early-onset CRC are treated in the adjuvant and metastatic setting, just as their older counterparts are.
- Fertility, pregnancy, sexual health, financial toxicity, and long-term survivorship challenges are some of the unique issues in the management of early-onset CRC.

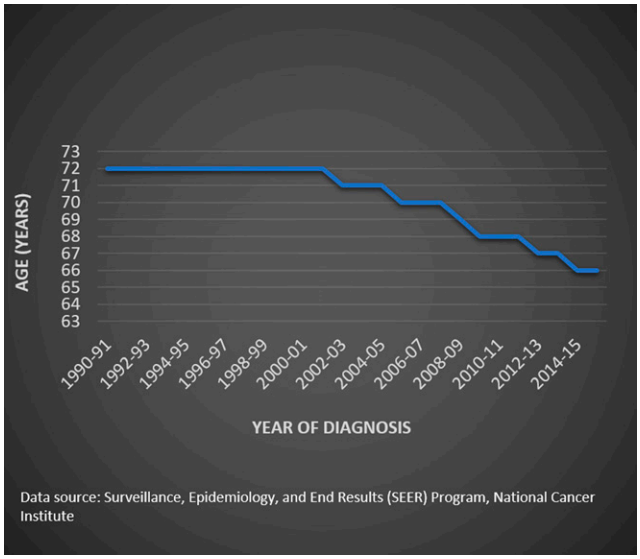

FIGURE 1. Median Age at Colorectal Cancer Diagnosis in the United States, 1990–2016

RISK FACTORS OF EO-CRC

A strong birth cohort effect indicates population-level changes in behavioral factors that influence cancer risk. Major established modifiable risk factors for CRC are excess body weight,[15] cigarette smoking,[16] heavy alcohol consumption,[17] a high intake of red or processed meat,[18] and physical inactivity.[19] Importantly, however, these associations are based almost entirely on cancer occurrence in older cohorts. The risk of EO-CRC among U.S. women was recently shown to have increased by 20% for every 5-unit increase in body mass index and by 69% for more than 14 hours per week of television watching.[20,21] An analysis of data on CRC in people younger than age 45 from two European case-control studies found relative risks for other modifiable factors similar to those in older patients.[22] However, a recent retrospective study of patients diagnosed at a New York academic center found no significant associations between obesity, smoking, and diabetes and EO-CRC risk.[23] Although molecular and clinical characteristics in patients age 30 to 49 are similar to those in patients age 50 and older,[24] suggesting common carcinogenic pathways, there remains an urgent need for research on the influence of new, highly prevalent early-life exposures on CRC risk.[25] For example, associations have recently been reported between colorectal tumors and antibiotic use as well as high-fructose corn syrup, probably mediated by alterations in the composition of gut microbiota.[26-28] The role of dietary components in regulating the microbiome and its impact on cancer risk is an area of active scientific study.[29-31]

The strongest known risk factor for CRC is a family history of the disease. People with a first-degree relative (FDR) who has been diagnosed with CRC have two to four times the risk of someone without this family history, with higher risk for diagnosis before age 50 and multiple affected relatives.[32] A CRC history among more distant relatives is also associated with increased risk,[33] as is a family history of adenomas.[34] More than one-quarter of patients younger than age 50 have an FDR with a history of CRC or adenomas, and an additional 16% have a hereditary syndrome, half of whom have Lynch syndrome.[35,36] People with Lynch syndrome are also at elevated risk for many other cancers, including endometrial, ovarian, small intestine, stomach, urinary bladder, and female breast.[37] Although rigorous colonoscopy surveillance leads to early-stage CRC diagnosis and high survival,[38] most of the estimated 1.2 million Americans (1 in 279) who have Lynch syndrome are undiagnosed.[39] For this reason, the National Comprehensive Cancer Network and ASCO recommend universal testing for Lynch syndrome in patients with CRC or endometrial cancer.[40,41] However, implementation of screening has been slow in the community setting,[42] despite coverage by most major public and private insurers.[43] Identification of high-risk families in the absence of a genetic syndrome also offers substantial opportunity to mitigate the cancer burden through early screening. However, a major obstacle is incomplete patient family history in medical records. One study found that less than half of primary care physicians document information about family members other than FDRs, and age at cancer diagnosis, which is a crucial indicator of disease risk, was rarely collected.[44] Another study found that only 22% of the medical records of patients with CRC had family history

information sufficient to identify people who should be referred for genetic counseling or testing.[45]

Although a larger proportion of early CRCs are hereditary compared with late CRCs, the majority of cases are sporadic (i.e., occur in average-risk patients). CRC is the most commonly diagnosed cancer and the leading cause of cancer death in men younger than age 50, whereas in women it ranks fourth (after breast, thyroid, and melanoma) and second (after breast) in terms of incidence and mortality, respectively.[46,47] Although the absolute risk of a CRC diagnosis by age 50 remains low (0.4% vs. 3.3% from age 50 to 85),[48] the burden for young adults is substantial and growing (Fig. 2). In 2020, 17,930 (12%) of the estimated 147,950 cases of CRC in the United States will be diagnosed in people younger than age 50—the equivalent of approximately 50 per day, in addition to 3,640 (of 53,200) CRC deaths in that age group.[12] According to cancer registry data covering more than 96% of the U.S. population, the age-standardized CRC incidence rate in ages 20 to 49 between 2012 and 2016 ranged from 30 (per 100,000) in Alaska Natives to 14 in blacks, 13 in non-Hispanic whites, and nine in Hispanics and Asian and Pacific Islanders.[47] However, rectal cancer incidence rates are now slightly higher in non-Hispanic whites (5.1 per 100,000) than in blacks (4.5 per 100,000) because of the rapid increase in the incidence of these tumors among whites.

SCREENING GUIDELINES: TIME FOR A CHANGE?

The majority of people diagnosed with CRC before age 50 are at average risk with respect to screening,[23,35] and half (48%) of these patients are age 45 to 49.[47] Most organizations, including the U.S. Preventive Services Task Force (USPSTF), recommend screening average-risk adults for CRC with colonoscopy (every 10 years), sigmoidoscopy (every 5 years), or stool testing (annually) beginning at age 50.[49-51] However, in 2018 the American Cancer Society prompted substantial controversy by lowering their recommended age to begin from age 50 to age 45.[52-54] The revision was based on an extensive review of empiric evidence on disease risk and the benefits and harms of screening, along with results from two simulation models from the Cancer Intervention and Surveillance Modeling Network that compared numerous combinations of screening strategies with regard to age to begin and end screening, type of test, and test interval. These models were the same as those used to inform the 2016 USPSTF recommendations but with an adjustment to account for the recent increase in underlying risk of CRC. Two of three unadjusted Cancer Intervention and Surveillance Modeling Network models used to inform the 2016 USPSTF recommendations found that screening beginning at age 45 rather than age 50 resulted in a more favorable balance of benefit to harm,[55] but the USPSTF resisted the change, citing a modest gain in life years, discord between the simulation models, and lack of empiric evidence to support screening among people in their 40s. Table 1 outlines recommendations regarding age to initiate CRC screening according to different patient risk categories.

Findings from recent studies support screening before age 50. Although data on colonoscopy outcomes among people younger than age 50 are limited, average-risk adults age 40 to 49 appear to have prevalences of any adenoma (14%–16%), large polyps (3%–4% in women and in 5%–6% men), and distal large polyps (5%) similar to those observed among adults age 50 to 54.[56-58] In addition, there is a higher burden of prevalent CRC in people age 45 to 49 than what is suggested by observed incidence rates, as indicated by the pronounced spike in incidence between age 49 and 50 upon screening initiation.[59] Recent studies have also shown screening beginning at age 40 or 45 to be cost effective.[60,61] Although health insurance coverage for average-risk screening before age 50 is variable, changes to USPSTF guidelines, expected in 2020 or 2021, could eliminate that obstacle, because the Affordable Care Act requires coverage for USPSTF-recommended preventive services.

Screening before age 50 is universally recommended for people at elevated risk of CRC because of familial syndromes (e.g., familial adenomatous polyposis, Lynch), chronic inflammatory bowel disease, or a family history of CRC or adenoma.[50,51] In addition, some organizations recommend beginning screening at age 45 for African Americans and Alaskan Natives because of their elevated risk.[51,62] It is noteworthy that, in recent years (2015–2016), incidence rates among non-Hispanic whites age 20 to 49 are the same as those among blacks (14.1 per 100,000).[12]

On the basis of national estimates, 13% of people age 40 to 44 and 21% of adults age 45 to 49 met the definition for up-to-date screening in 2018 compared with 67% of those age 50 and older.[12] CRC screening test use among people in their 40s is more common for those with a family history, although less than half of people with an FDR report screening, and most (> 80%) of those who are tested in their 40s have no family history.[63,64] Blacks age 45 to 49 are approximately 30% more likely than whites to have had a recent colonoscopy because of the long-standing recommendation for screening in this population.[64] Patterns of CRC screening test use do not appear to explain the increase in EO-CRC through lead-time bias, as previously hypothesized.[65] Past-year colonoscopy use in people age 40 to 44 remained steady at 3% from 2000 to 2015, despite a 28% relative increase in CRC incidence, whereas prevalence doubled among people age 45 to 49, but CRC incidence was stable for localized tumors and increased only for advanced disease.[64] Among people age 40 to 49,

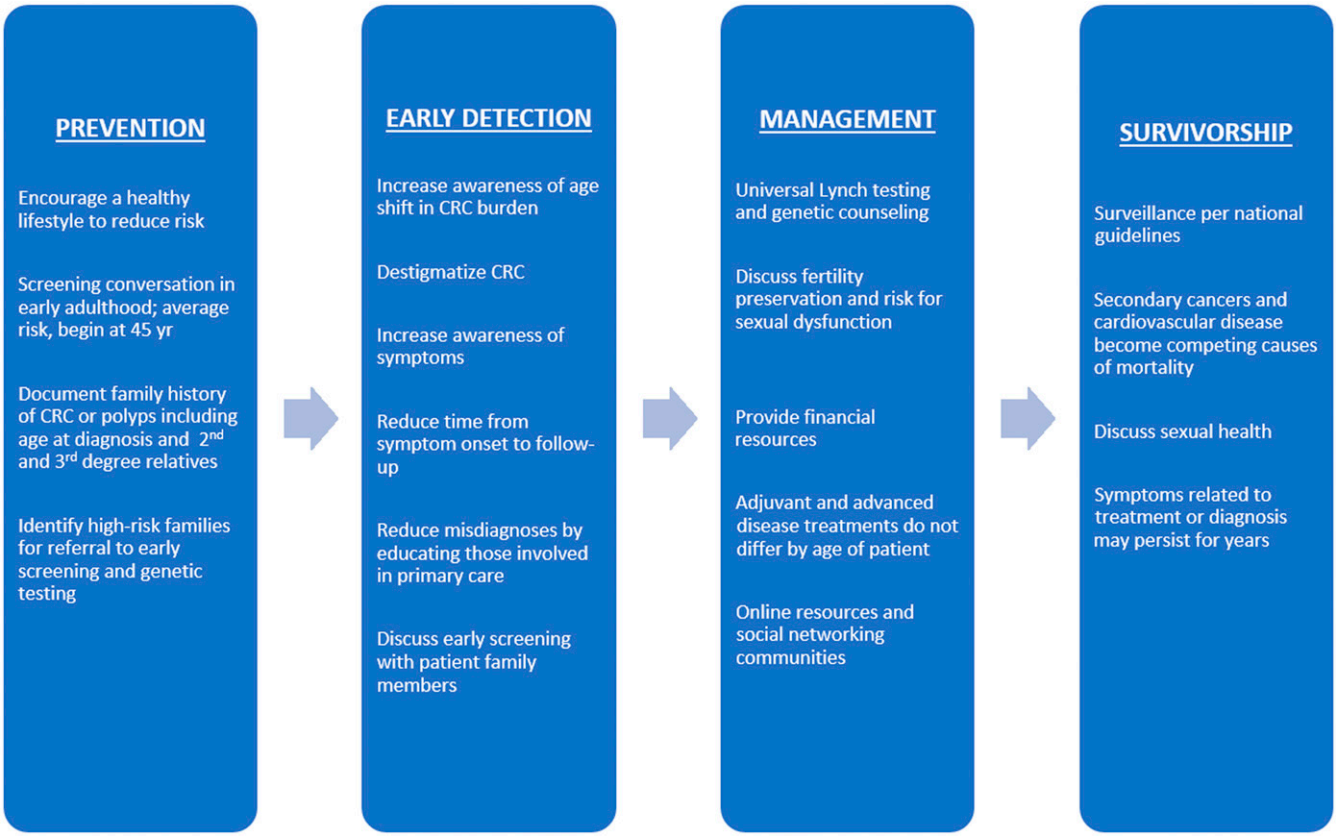

FIGURE 2. Opportunities for Mitigating the Burden of Colorectal Cancer Among Patients Younger Than Age 50 Across the Cancer Continuum

increasing incidence is limited to advanced-stage disease.[7] The 5-year survival rate among patients with EO-CRC decreases from 94% for localized-stage disease to 21% for distant-stage diagnoses.[12] Young patients are diagnosed at a later stage than older patients, even when screening-detected cancers are excluded.[66]

OPPORTUNITIES TO REDUCE CRC IN THE YOUNG WITH CHANGES IN SCREENING

Most current guidelines recommend the initiation of screening for average-risk patients at age 50 (USPSTF, the Canadian Task Force on Preventive Health Care, the European Council, the American Academy of Family Physicians, and the American College of Physicians).[49,67] However, it is becoming increasingly recognized that sporadic EO-CRC represents a large number of CRC cases, with growing morbidity and mortality, because these patients present more often with stage III or IV disease. The biggest increases in CRC are occurring among people younger than age 40, which suggests that consideration should be given to starting screening at age 40.[2,4,5] Cancer screening models must be updated with the most current data regarding age and incidence of CRC. The American Cancer Society has shown leadership on this issue, with a recent update to their model and screening guidelines released in 2018 that recommend starting screening at age 45 for the normal-risk population.[68] It is imperative to continue to reassess epidemiology data and screening guidelines for at-risk populations; currently, the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy support screening from age 45 for African Americans.[69] In addition, the U.S. Multi-Society Task Force of Colorectal Cancer recommends screening at age 40 for all patients with a family history of CRC at any age.[70] Incidence data must continue to be analyzed and mined to ensure appropriate threshold ages for beginning of screening.

OTHER POPULATIONS TO TARGET

First-Degree Relatives With Adenomas

Taking advantage of our understanding of the continuum of colorectal tissue neoplasia, which has a well-described progression from adenoma to dysplasia to carcinoma, we have an opportunity to modify screening recommendations for patients with a family history of polyps to potentially capture patients at an earlier, benign point in this sequence.[71,72] A large proportion of patients with sporadic EO-CRC have a family history of advanced polyps.[36] Accordingly, clinicians should include not only CRC but also

TABLE 1. Age to Initiate CRC Screening Based on Risk Category

Risk Category	Family History	Age to Initiate Screening	Recommended Test
"Average" Risk (no known family history)		Age 50[a-g] Age 45[h]	Colonoscopy (every 10 years), sigmoidoscopy (every 5 years), multitargeted stool DNA (every 3 years), or fecal occult blood test or FIT (annually)
African American or Alaskan Native Who Are at "Average" Risk		Age 45[f]	
Familial Adenomatous Polyposis		Age 10–12[g]	Colonoscopy (annually until colectomy)
Lynch Syndrome		Age 20–25 or 2–5 years younger than youngest age at diagnosis of CRC in family if diagnosis before age 25[f]	Colonoscopy (every 1–2 years)
Inflammatory Bowel Disease		8 years after disease onset[g]	Colonoscopy (every 1–3 years)
Relative With CRC	Cancer in an FDR	Age 40 or 10 years younger than age of diagnosis of FDR[f,g]	Colonoscopy every 5 years
	Cancer in $\geq$ 2 SDRs	Age 40[f]	
FDR With Advanced Colorectal Polyp	Advanced adenoma in 1 FDR $<$ 60 years or in 2 FDRs	Age 40 or 10 years younger than age of diagnosis of FDR[f]	Colonoscopy every 5 years
	Advanced adenoma in 1 FDR $\geq$ 60 years	Age 40[f]	Colonoscopy every 10 years or FIT annually
	Confirmed advanced polyp in 1 FDR (any age)	Age 40 or at age of diagnosis of advanced adenoma in FDR[g]	Colonoscopy every 5–10 years

Abbreviations: CRC, colorectal cancer; FDR, first-degree relative; FIT, fecal immunochemical testing; SDR, second-degree relative.
[a]U.S. Preventive Services Task Force.
[b]Canadian Task Force on Preventive Health Care.
[c]European Council.
[d]American Academy of Family Physicians.
[e]American College of Physicians.
[f]U.S. Multi-Society Task Force of Colorectal Cancer, which represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.
[g]National Comprehensive Cancer Network.
[h]American Cancer Society.

a family history of advanced colorectal polyps in an assessment of a patient's risk.

Currently the U.S. Multi-Society Task Force of Colorectal Cancer, American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy recommend advanced screening for patients who have an FDR with an advanced adenoma before age 60; these recommendations include screening colonoscopy at age 40 or 10 years younger than age of diagnosis of advanced adenoma in the FDR, with follow-up colonoscopy every 5 years. The National Comprehensive Cancer Network recommends starting screening at age 40 for patients with an FDR with a history of advanced polyps at any age.[73]

All young adults should be counseled to speak to their family regarding their history of advanced polyps so that they can be considered for earlier screening or other interventions. The National Colorectal Cancer Roundtable created the Advanced Colorectal Polyp GI Brief to provide endoscopists and primary care clinicians with a resource to help treat patients with advanced polyps.[74,75] One suggestion is for endoscopists to draft a personalized letter detailing patient colonoscopy results, follow-up, and risk factors so that patients are more likely to share this information with relatives about potential screening implications.[76]

Overall, the guidelines from the American Cancer Society, the U.S. Multi-Society Task Force of Colorectal Cancer, and the American College of Radiology for FDRs with adenoma are identical to the recommendations for an FDR with CRC before age 60.[77] However, the USPSTF currently does not support this recommendation, because it could overwhelm screening capacity because of the high prevalence of adenomas in the age 50 to 59 population and because there

was insufficient evidence that increased screening would reduce mortality.[49,78]

Other Risk Factors

There is also a real opportunity to improve outcomes in EO-CRC by maximizing compliance in populations in which guidelines already recommend early screening. Studies have suggested that there is often poor adherence to early screening among patients with known cancer syndromes or familial CRC, especially among those at low socioeconomic levels for many reasons, including distrust of the medical community, poor access to health care, and uncertainty in navigating the health care system.[79] Interventions aimed at educating patients and providers about recommendations and resources, including social work and patient navigator supports, could result in significantly increased compliance with screening recommendations. Another group at elevated risk that should be considered for early screening is those who have received pelvic radiation in adolescence or early adulthood. Finally, with the predominance of left-sided or rectal cancers in EO-CRC, sigmoidoscopy screening initiated at an earlier age could be another screening solution.[80]

BARRIERS TO CARE

Beyond increasing appropriate screening and surveillance, there is an immediate opportunity to reduce mortality through earlier diagnosis. One single-institution study found a median time from onset of rectal cancer symptom to treatment of 217 days for patients younger than age 50 compared with 29.5 days for those older than age 50, largely because of patient delays in presentation to the initial physician.[81] Some of these delays are caused by misdiagnoses.[82] Patient-based delays in seeking care may be related to poor knowledge of worrisome symptoms, embarrassment, denial, low health literacy, and poor social and family support. Additional factors include lack of access to health care (e.g., being uninsured or underinsured) and poor access to transportation. More challenging to quantify in terms of effect, younger patients may have competing demands of time with familial and employment responsibilities that supersede attention to personal health.

Patients with EO-CRC can present with characteristic symptoms, including abdominal pain, weight loss, and fatigue, but tend to have a higher rates of left-sided related symptoms at presentation, including rectal bleeding and changes in bowel habits.[2,83,84] Diagnosis can be delayed because symptoms are attributed to a low index of suspicion on the part of treating providers, who focus on more common conditions in young adults.[85,86] A recent study found that, among the 52% of patients with EO-CRC who experienced rectal bleeding, the average time from onset of bleeding to diagnosis was 271.17 days.[87] This challenge can be addressed by working with national primary care groups to educate the provider community about the changing incidence of this entity. Primary care physicians and other clinicians can have a dramatic impact on the morbidity and mortality of EO-CRC by ruling out serious causes of these symptoms in young patients (rectal bleeding, abdominal pain, change in bowel habits, and anemia).[88-90] Indeed the American Society for Gastrointestinal Endoscopy recommends endoscopic evaluation of all patients with lower gastrointestinal bleeding.[91] Although diagnosis delays do not completely account for the disproportionate distant-stage disease in young patients,[66] improving access to care and educating patients and clinicians about the symptoms of CRC would undoubtedly improve outcomes in this population.[92]

TREATMENT AND CARE CONSIDERATIONS IN YOUNG PATIENTS WITH CRC

Several reviews have systematically examined and summarized studies related to prognosis and treatment outcomes in EO-CRC.[93,94] As previously described, younger patients are more likely than their older counterparts to present with advanced regional or distal disease. Compared with older patients, patients with EO-CRC have higher cancer-specific survival at every stage, despite usually high-risk pathology, as indicated by population-based studies.[12,93] This difference may reflect fewer comorbidities or more aggressive treatment regimens. In the metastatic setting, patients with EO-CRC treated with standard regimens or clinical trials can have poorer progression-free survival but do not have worse overall survival or response rates.[95,96] Patients with EO-CRC are more likely to receive additional surgical therapy for both early-stage and metastatic disease, potentially reflecting both patient and provider age-related biases.

Current national and international guidelines do not have different treatment recommendations for patients with EO-CRC and patients with later-onset CRC, but a more aggressive treatment paradigm is often pursued. Multiple studies describing adjuvant approaches with more aggressive systemic cytotoxic regimens, targeted agents, or surgical approaches differing from current guidelines have led to potential overtreatment with unclear benefits.[97-102] Younger patients can be overtreated because oncologists perceive them to have fewer adverse reactions to chemotherapy, fewer comorbidities, and a worse prognosis at diagnosis.

Early-Stage Disease

Compared with an older cohort (age 65–75), more patients with early-stage EO-CRC (age 18–49) are given adjuvant therapy for stage II and III disease, including low- and high-risk stage II disease.[101,103] Kneuertz et al[101] reported that patients with stage II low-risk EO-CRC receive adjuvant therapy 50% of the time, compared with 19.1% in the 65- to

75-year-old cohort, with no improved survival in younger patients. Another study using the National Cancer Database analyzed more than 40,000 patients with early-stage CRC to examine differences in characteristics of patients with CRC younger than age 50 compared with those older than 50. It found that patients with EO-CRC were more likely to receive National Comprehensive Cancer Network guideline–driven care but had no survival advantage as a result. Alternatively, in the cohort of patients older than age 50, those who received guideline-driven care had better survival than those who did not.[104]

There have also been studies examining the efficacy of specific systemic agents based on age. An analysis of patients younger than age 60 from the CAO/ARO/AIO-04 (Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society), randomized, phase III trial showed that adding oxaliplatin to 5-fluorouracil–based adjuvant chemotherapy reduces local and distal recurrence in this younger cohort, similar to the entire cohort in the original study results.[105] Regarding targeted agents in the adjuvant space, when cetuximab or bevacizumab is added to adjuvant fluorouracil, leucovorin, and oxaliplatin regimens, there is no increase in survival, although younger patients seem to tolerate multiagent regimens better than their older counterparts.[97-99,102]

Advanced and Metastatic Disease

Recommendations for the treatment of metastatic disease are the same regardless of age. For patients with EO-CRC, one should consider assessment of performance status, comorbidity, *RAS*/*BRAF* status, and primary tumor sidedness. Regarding specific regimens, outcomes in the cohort younger than age 50 from nine phase III, fluorouracil-based, single-agent and combination studies were analyzed by Blanke et al.[95] They concluded that patients with EO-CRC had lower progression-free survival but no difference in relative risk of death or overall survival compared with the cohort of patients older than age 50, a finding that persisted whether the age cutoff was 40 or 50 years. Of note, nausea was more likely in younger cohorts, but diarrhea and neutropenia were less common. Another systematic review looked at 24 first-line clinical trials, including trials with double and triple therapy and targeted agents. The trials included 3,051 patients in total, 15% of whom were younger than age 50. They concluded that the youngest (closer to age 20) and oldest (older than approximately age 65) cohorts had the lowest progression-free and overall survivals.[96]

MOLECULAR BIOLOGY CONSIDERATIONS

Regarding sidedness and mutations in the KRAS–NRAS–BRAF pathway, multiple studies have suggested a similar proportion of *KRAS* mutations in EO-CRC, but there are some outliers.[106,107] A genetic study from France sequenced 39 patients with sporadic EO-CRC (before age 45) for *TP53*, *KRAS*, *BRAF*, and *PIK3CA* mutations and the presence of a methylator phenotype. Gene expression studies were also performed to elucidate activated cellular pathways in these samples. They found fewer *BRAF* mutations, fewer methylator phenotypes, and upregulation of certain signaling pathways (Wnt/beta catenin, MAP kinase, growth factor signaling, TNFR1 pathway), suggesting that EO-CRC may be a distinctive molecular entity.[108] Another study looking at tumors from patients age 30 or younger found that microsatellite instability in EO-CRC was more prevalent, was not tightly linked to *MLH1*/*PMS2* loss, and was never associated with $BRAF_{V600E}$ mutations.[100] These were small studies, and larger trials will be needed to truly assess the molecular differences between younger and older patients with CRC. A recent study of more than 36,000 patients with CRC in four study cohorts found that the continuum of clinical and molecular age-associated differences slows after age 30 and that characteristics of patients age 40 to 49 are very similar to those of patients age 50 to 59.[24]

ADDITIONAL CARE CONSIDERATIONS IN PATIENTS WITH EO-CRC

Sexuality

With a rise in EO-CRC, there is a clear need to identify and address survivorship concerns that are unique to younger adults who may be married, unmarried, dating, or still exploring their sexuality. Sexual health is often neglected yet critically important for patients with EO-CRC, who may be reluctant to talk to their health care teams or unaware that interventions for sexual challenges may be available. A cross-sectional study in France of patients with CRC ages 20 to 84 found that only 20% of men and 11% of women—11% with colon cancer, and 33% with rectal cancer—discussed sexuality with their cancer team, although younger patients (< age 55) received more information than their older counterparts.[109]

Studies have shown that patients with CRC have higher rates of sexual dysfunction than the general population and are less sexually active after surgery. Female patients may face vaginal reconstruction, dryness, or pain during intercourse, and male patients may experience erectile dysfunction. Overall, women and patients with rectal cancer appear to report more sexual and body image distress than men or those with colon cancer.[110] The type of surgery can have an impact, as one study reported that women who underwent abdominoperineal excision were less sexually active than women who underwent lower anterior resection.[111,112] Among men, erectile dysfunction was reported as a symptom in 54% of rectal cancer survivors and 25% of colon cancer survivors.[111] Presence or history of ostomy is another important factor in sexual outcomes and body image. One

survey study found that patients with current or past ostomy reported worse sexual function, and those with a current ostomy struggled more with body image issues than those who never had an ostomy.[113]

As the number of patients with EO-CRC increases, there is a need to better understand and preserve a patient's sexual health after treatment, surgery, and radiation. It is critical that we empower and encourage patients, caregivers, and medical teams to proactively discuss sexual health and long-term post-treatment side effects for patients with EO-CRC. Communication and assessment and tools are available.[114-116] After discussions, interventions can be explored, including long-term counseling, vaginal lubricants, or topical estrogen for women and phosphodiesterase-5 inhibitors and testosterone replacement for men.[117]

Fertility

Fluorouracil is the backbone of chemotherapy in the adjuvant and metastatic settings. It has been shown to reduce sperm count temporarily and may also cause amenorrhea, although risk is low.[118] For other treatments commonly used in CRC, such as oxaliplatin, irinotecan, and anti-EGFR and -VEGF therapy, effects on fertility are largely unknown. However, radiation can result in decreased or eradicated fertility and early menopause if the radiation field contains the ovaries or uterus, and it can result in decreased male fertility through prostatic and gonadal radiation.[118]

Pregnancy

CRC can occur during pregnancy and may be a more common occurrence with delays in childbearing. An article outlining CRC systemic treatments and their potential risk during pregnancy listed each as having either a C or D pregnancy risk category. Category C is defined as treatments for which animal studies have shown adverse effects on the fetus and for which there are no adequate studies in humans. Category D is defined as treatments for which there is evidence of human fetal risk according to data from investigational or marketing experience or studies in humans. For both categories, the benefits of the drug must be balanced against risks. Select cases and outcomes of patients and infants were described.[119] Important recommendations included avoiding systemic agents as much as possible during the first trimester and avoiding targeted agents altogether because of the lack of studies in pregnant patients. Both fluorouracil and oxaliplatin have been given in the second and third trimester, but the risks and benefits for the mother must be weighed carefully, with close involvement of high-risk maternal-fetal medicine.

Financial Toxicity

The topic of drug costs and comprehensive cancer care is not often raised with patients in their doctors' offices or elsewhere. Patients with and without insurance are facing increasing out-of-pocket expenses because of coinsurance, copays for expensive cancer drugs, and—in some cases—drugs that are not covered by insurance. Young cancer survivors are more likely to experience material (e.g., trouble paying bills), psychological (e.g., worrying about paying bills), and behavioral (e.g., skipping medications) financial hardships. For example, in a nationally representative survey, more than 43%, 54%, and 31% of cancer survivors younger than age 50 reported material, psychological, and behavioral effects of medical financial hardship, respectively—rates that were higher than those of older cancer survivors and cancer-free counterparts.[120] We must expand our vocabulary to include financial toxicity as a real problem that patients face as a result of a cancer diagnosis and consider cost when designing a treatment plan.

The pace of increasing financial toxicity is alarming, especially for young patients with CRC. Among young patients and survivors of cancer (age $<$ 40), financial toxicity as measured through an 11-item distress survey was found to be associated with lower insurance satisfaction, more depression and anxiety symptoms, and lower coping with cancer. Furthermore, financial toxicity leads to skipping or delaying treatment in multivariable modeling.[121] Patients at the highest risk for financial toxicity are those in the lowest income quartile and those who undergo emergency surgery, are black or Hispanic, and undergo surgery for esophageal or colon cancer.[122]

Many young patients are juggling competing financial priorities and have the added stress of increasing out-of-pocket medical costs during treatment. Among patients with stage III colon cancer undergoing adjuvant chemotherapy, studies find that younger age and lower household income are strongly associated with financial hardship, and 40% of the patients accessed money from savings accounts during treatment.[123,124] In addition to direct monetary costs, the burden includes patient time costs, including time receiving care rather than working or engaging in other activities. Depending on the type of cancer and phase of care, patient time costs range from hundreds to many thousands of dollars per year. In addition to direct costs, patients may also face indirect costs through lost wages and lower earning potential and may experience job loss or job lock (i.e., being unable to change jobs) because of concerns about health insurance coverage.[125]

We must seek opportunities to openly discuss and address financial hardship for patients and their families. Furthermore, we need policy makers to explore new strategies to lessen the economic impact of new CRC therapies, such as easing restrictions on the federal government's ability to negotiate drug prices and asking drug developers to reassess pricing policies. Evidence-based interventions and patient assistance programs can provide real and

substantive support for families. It is therefore paramount that advocacy organizations, such as Fight Colorectal Cancer, the American Cancer Society's Action Network, the Prevent Cancer Foundation, and Friends of Cancer Research, engage in a national dialogue with all stakeholders, including health care providers and systems, payers, and patients, to tackle together the unique challenges faced by patients with EO-CRC.

Survivorship

Fortunately, 5 years after curative treatment, the most common cause of death for EO-CRC survivors is the same as for any other person of that age.[126] Over time, secondary cancers become a more common cause of death and the eventual leading cause of death 11 to 15 years after treatment. Cardiovascular disease also becomes an increasingly important cause of death further from treatment.[126] Still, there is a large and growing population of patients with EO-CRC who are treated for early-stage disease and survive long term. Survivors may experience chronic side effects after surgery, radiation, and chemotherapy that can last through the remainder of life. Persistent symptoms may include fatigue, anxiety, sleep dysfunction, genitourinary problems, bone problems, psychological and body image problems, long-term pain, bowel problems, and neuropathy along with secondary cancer risk.[127,128]

One study comparing long-term symptoms (assessed at a mean time of 10.8 years since cancer) by age found that younger survivors (age 18–50) had higher scores for anxiety, body image problems, abdominal and pelvic pain, bloated feeling, hair loss, and embarrassment related to bowel movements.[129] Quality of life (QOL) assessments of CRC survivors reveal high health-related and global QOL scores and are similar to those of older age groups (< 60 vs. > 70). However, young survivors tend to report lower scores in social functioning. QOL has been found to be most affected by higher residual symptom burden, rectal cancer, lower education level, and ostomy presence. In one cohort, higher QOL was associated with improved survival, and the highest-scoring patients had the lowest all-cause mortality.[130,131] However, there is a paucity of research focusing on survivorship issues specifically in patients with EO-CRC. Considerations include surveillance and radiation exposure, recommended lifestyle changes, and preventive modalities for patients with EO-CRC as well as the mental and social implications of survivorship and the impact on family.[132] This is a large unmet need for which funding should be prioritized nationally.

Role of Advocacy Groups and Social Media

Advocacy groups provide vital information for young men and women with CRC, along with their family and friends. These efforts often leverage survivor stories to raise awareness and encourage education about EO-CRC, covering a variety of topics in addition to disease and treatment information, such as patient stories related to dating, family, and sexuality.[133] Advocacy organizations also provide resource libraries with information about clinical trials and financial and insurance assistance. Examples of advocacy groups with a strong social media presence include COLONTOWN, the Colon Club, Colon Cancer Coalition, Fight Colorectal Cancer, the Colon Cancer Foundation, Colorectal Cancer Alliance, and Michael's Mission. COLONTOWN is an online community of patients and survivors with different "neighborhoods," including Youngstown (patients younger than age 40), Poker Club (male patients only), Tough Chicks (women only), and PTA (patients with young children).[134] The Colon Club features a magazine highlighting survivors younger than age 50 and their caregivers, called "On the Rise."[135] Large advocacy groups, such as the Colon Cancer Coalition, Colorectal Cancer Alliance, and Fight Colorectal Cancer, have website subsections devoted to EO-CRC awareness and symptoms along with patient testimonials.[136-138] The Colon Cancer Alliance regularly conducts and publishes results from a survey of patients with EO-CRC, survivors, and their caregivers to better understand and support this growing population, including information on the most common symptoms, delays in diagnosis, and QOL. The 2018 report, based on information from more than 1,600 respondents in 38 countries, found that 80% of patients with EO-CRC had children younger than age 18 at the time of diagnosis.[139] There are also an increasing number of large scientific meetings dedicated to EO-CRC, including the yearly Early Age Onset Colorectal Cancer Summit, which is hosted by the Colon Cancer Foundation in partnership with the Colon Cancer Coalition.[140]

CONCLUSIONS

EO-CRC is an increasing public health problem, with major ramifications for patients and their families. Approximately 30% of rectal cancer is diagnosed in patients younger than age 55, and recent work showing a surge of CRC diagnosed at age 50 (when screening begins) compared with age 49 suggests strongly that patients younger than age 50 already are at increased risk of having precancerous polyps and cancer. The American Cancer Society has taken leadership on this issue and recommends that screening begin at age 45 for the average-risk population, a qualified recommendation only because there is a lack of information on screening for patients younger than age 50 to confirm efficacy. Other national guideline bodies similarly should reassess recent data in their calculations and recommendations.

There are unique clinical challenges for patients with EO-CRC. Diagnostic delays result from low indices of suspicion from primary providers, financial toxicity for patients who are

in the prime of their earning potential, sexual and fertility considerations, and long-term survivorship concerns. Focused support for patients with EO-CRC is needed during their therapy and survivorship, as well as education for primary providers and oncologists on diagnosing and caring for survivors over the long term. Finally, we need more research exploring the etiology of this entity so that we can improve treatment and management for this particular CRC population. Together, these steps will allow us to work together as a medical community to improve outcomes for our patients with EO-CRC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_279901.

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