The Increasing Incidence of Young-Onset Colorectal Cancer: A Call to Action

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Abstract

In the United States, colorectal cancer (CRC) is the third most common and second most lethal cancer. More than one-tenth of CRC cases (11% of colon cancers and 18% of rectal cancers) have a young onset (ie, occurring in individuals younger than 50 years). The CRC incidence and mortality rates are decreasing among all age groups older than 50 years, yet increasing in younger individuals for whom screening use is limited and key symptoms may go unrecognized. Familial syndromes account for approximately 20% of young-onset CRCs, and the remainder are typically microsatellite stable cancers, which are more commonly diploid than similar tumors in older individuals. Young-onset CRCs are more likely to occur in the distal colon or rectum, be poorly differentiated, have mucinous and signet ring features, and present at advanced stages. Yet, stage-specific survival in patients with young-onset CRC is comparable to that of patients with later-onset cancer. Primary care physicians have an important opportunity to identify high-risk young individuals for screening and to promptly evaluate CRC symptoms. Risk modification, targeted screening, and prophylactic surgery may benefit individuals with a predisposing hereditary syndrome or condition (eg, inflammatory bowel disease) or a family history of CRC or advanced adenomatous polyps. When apparently average-risk young adults present with CRC-like symptoms (eg, unexplained persistent rectal bleeding, anemia, and abdominal pain), endoscopic work-ups can expedite diagnosis. Early screening in high-risk individuals and thorough diagnostic work-ups in symptomatic young adults may improve young-onset CRC trends.

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SPECIAL ARTICLE
in all 5-year age groups between 20 and 49 years, with the sharpest increases among individuals 40 to 44 years old (10.7 per 100,000 population in 1988 and 17.9 per 100,000 population in 2006). In the National Cancer Database, a hospital-based cancer registry capturing 70% of all incident cancers in the United States, young-onset CRC incidence increased from 1998 to 2007 (annual percent change [APC], 2.1%; 95% CI, 1.1%-3.1%), whereas later-onset incidence decreased (APC, −2.5%; 95% CI, −3.0% to −2.0%). As in SEER, young-onset rectal cancer incidence (APC, 3.9%; 95% CI, 3.1%-4.7%) increased more rapidly than young-onset colon cancer (APC, 2.7%; 95% CI, 2.0%-3.3%). Compared with later-onset disease, young-onset CRC was more common among nonwhite individuals and among those who were either uninsured or Medicaid insured.

The CRC mortality trends mirror incidence trends. Age-adjusted young-onset CRC mortality rates in 2005-2009 ranged from 0.2 per 100,000 population (ages 20-24 years) to 7.7 per 100,000 population (ages 45-49 years). The mortality rate for those with young-onset CRC remained stable between 1975 and 2004, then increased by approximately 2% annually through 2009. By contrast, the age-adjusted mortality rate in older individuals decreased by 2% to 3% annually between 1992 and 2009.

**WHY IS YOUNG-ONSET CRC INCREASING?**

Drivers of increasing young-onset CRC incidence are not well understood. In the absence of rigorous epidemiologic studies, it is noteworthy that young-onset CRC incidence increased, whereas CRC risk factors, such as sedentary lifestyle, obesity, and diabetes mellitus, were common or increasing. Each 5-unit increase in body mass index is associated with an estimated 13% to 18% increase in CRC risk. Diabetes mellitus has been associated with up to a 38% (summary relative risk 95% CI, 1.26-1.51) increase in colon cancer risk and a 20% increase in rectal cancer risk (95% CI, 1.09-1.31). Similarly, regular physical activity is associated with a 24% to 31% reduction in CRC risk. These risk factors alone do not explain the observed trends in young-onset CRC because they are common or increasing in older age groups in which CRC incidence decreased.

Screening for CRC in average-risk individuals is credited as the largest single driver of decreasing CRC incidence and mortality overall. From 1990 to 2010, screening adherence increased to approximately 65% for individuals 50 to 70 years old, with concurrent decreases in CRC incidence. Average-risk screening is generally only recommended for individuals after 50 years of age. The fact that routine screening is largely confined to those older individuals might partially explain age-related disparities in CRC incidence and mortality trends. Additional epidemiologic research is needed, however, to better understand these trends.

**DISTINCTIVE BIOLOGY AND GENETICS OF YOUNG-ONSET CRC**

Single-institution and population-based studies have found distinctive tumor location, stage at presentation, and histologic features in young-onset CRC. These tumors occur more often than later-onset tumors in the distal colon and the rectum (69.0% vs 57.7%, P<.001). In individuals 35 to 39 years of age, 32% of CRC...
tumors occurred in the rectum. The percentages decreased in subsequent age groups to a low of 15.1% in the 85 years and older group. The proportion of rectal cancers occurring in young individuals recently reached 18%.

Poorly differentiated histologic features and mucinous and signet ring features, which are common in young-onset disease, are typically associated with worse outcomes in CRC. In the National Cancer Database, mucinous and signet ring histologic subtype occurred more commonly in patients with young-onset CRC than in patients with older-onset CRC, although the differences were relatively small (12.6% vs 10.8%, \(P<.001\)). Similarly, in SEER data (1991-1999) young patients (ages 20-40 years) were more likely than older patients (ages 60-80 years) to have mucinous CRC tumors (15.7% vs 11.5%, \(P<.001\)); the corresponding rates for signet ring cell tumors were 3.8% and 0.8% \((P<.001)\). Tumors were also poorly differentiated in 27.3% of patients 20 to 40 years old vs 17.2% in patients 60 to 80 years old \((P<.001)\) and anaplastic in 1.6% of the younger cohort vs 0.7% of the older cohort \((P<.001)\). The reasons for these histologic differences are not yet known, but differences in the molecular biology of these tumors is one possible explanation.

Young age of CRC onset is one of the hallmarks of hereditary CRC syndromes, and these syndromes contribute disproportionately to young-onset CRCs. From a consecutive series of more than 1100 CRCs, Chang et al characterized 75 CRCs in patients younger than 40 years and found that 22% of these tumors were likely due to hereditary syndromes (17% due to abnormalities in DNA mismatch repair and 5% due to other genetic syndromes). Several studies have reported that the nonhereditary young-onset CRCs may have a unique molecular profile in that they are typically microsatellite stable (MSS) and have a lower frequency of aneuploidy and \(BRAF\) sequence variation, a lower frequency of the CpG island methylator phenotype, and a greater frequency.

**FIGURE 2.** Surveillance, Epidemiology, and End Results age-adjusted incidence per 100,000 individuals by age and year for colorectal cancer (A), colon cancer (B), and rectal cancer (C).
of hypomethylation of LINE than older-onset MSS CRCs.36-40

Young-onset CRC is more likely to be detected at an advanced stage. One large-scale study found that patients with young-onset CRC were significantly more likely to present with stage III/IV disease compared with patients with older-onset disease (colon cancer: 63.4% vs 49.0%, \(P<.01\); rectal cancer: 57.3% vs 46.2%, \(P<.01\)).10 Among patients with young-onset disease, advanced stage at diagnosis was more common in the youngest ages (ages 18-29 years: hazard ratio [HR], 1.4; 95% CI, 1.2-1.6; ages 30-39 years: HR, 1.2; 95% CI, 1.1-1.4; vs ages 40-49 years). Patients with young-onset CRC who were African American (HR, 1.2; 95% CI, 1.1-1.3; vs white race) and Medicaid insured or uninsured (uninsured: HR, 1.2; 95% CI, 1.1-1.3; Medicaid: HR, 1.6; 95% CI, 1.5-1.8; vs insured) were also more likely to present with stage III/IV disease.

Later stage at diagnosis, possibly related to lower screening rates and/or failure to recognize and evaluate colonic symptoms in younger individuals, is concerning because it likely leads to worse prognosis. SEER data (1991-1999) confirm that young (ages 20-40 years) patients with colon cancer have a poorer overall 5-year survival compared with their 60- to 80-year-old counterparts (61.5% vs 64.9%; \(P=.02\)). Stage-specific survival rates in patients with young-onset CRC, however, equal or exceed those of their counterparts with later-onset CRC, which may in part reflect a lower comorbidity burden and a tendency toward a higher treatment completion rate in younger patients (Table 1).13,41 The combination of a disproportionate share of Lynch syndrome and a poorly understood group of MSS diploid CRCs to young-onset CRCs may contribute to the higher frequency of poorly differentiated mucinous and signet ring cell CRCs without the worse prognosis usually associated with this histologic type. Ultimately, our knowledge regarding the molecular basis of most young-onset CRC remains limited, and more research in this area is needed.

### HIGH-RISK INDIVIDUALS: EARLY SCREENING FOR YOUNG ADULTS WITH FAMILY HISTORY. PREDISPOSING CONDITIONS, OR HEREDITARY SYNDROMES

A family history of CRC or advanced adenomatous polyps in a first-degree relative (FDR), particularly if the CRC occurred before 60 years of age, can increase an individual’s CRC risk up to 4-fold.42 Approximately 10% to 15% of American adults have at least 1 FDR with CRC and are therefore at increased risk for this disease (Table 2).42 Individuals with an FDR younger than 60 years diagnosed as having CRC should begin screening either at 40 years of age or 10 years earlier than the youngest age at CRC diagnosis for any affected FDR.13-46

Adherence to these guidelines requires PCPs to discuss CRC-related family history with patients before 40 years of age, an approach also consistent with the American College of Physicians’ recommendation to complete CRC risk assessments for all adult patients.46,47

Tools are available to help PCPs obtain a cancer-related family history and improve risk-based CRC screening. For example, the Office of the Surgeon General has developed a family history initiative portal to enhance the accuracy of the personal and family medical history.76 Similarly, the National Colorectal Cancer Roundtable’s PCP toolkit also provides clinical information, lists common errors physicians may make in risk assessment and screening recommendations, and notes that an office-specific CRC screening policy, reminder system, and communication strategy can improve screening adherence and outcomes.92

Young age at onset is a hallmark of hereditary cancer syndromes. In addition to the general familial risk factors listed in Table 3, PCPs should be aware of the 2 most common hereditary CRC syndromes: Lynch syndrome (also termed *hereditary nonpolyposis colorectal cancer*) and familial adenomatous polyposis (FAP). The median age at CRC diagnosis among individuals

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<tr>
<td>All</td>
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<th>Older (60-80 y)</th>
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*AJCC = American Joint Committee on Cancer; NS = nonsignificant.

Data from World J Surg.
with Lynch syndrome is 42 to 45 years, and 35% to 40% of individuals with this syndrome are diagnosed as having CRC before the age of 40 years. Many patients with hereditary nonpolyposis colorectal cancer will report a personal or family history that fulfills either the Amsterdam criteria or the Revised Bethesda Guidelines. Any patient who meets either criteria should be referred to a genetic counselor, who will typically conduct more detailed assessment of familial risk and, when appropriate, initiate tumor microsatellite testing, immunohistochemical analysis of the mismatch repair genes or proteins, and confirmatory germline testing.

Characterized by numerous (at least 100) adenomatous polyps in the large intestine, FAP affects approximately 1 in 15,000 to 1 in 8000 individuals, virtually all of whom will develop CRC by 50 years of age if left untreated. The median age for CRC development in this group of individuals is approximately 39 years; 7% have CRC by 20 years of age and 15% by 25 years of age. The median age for development of polyps in individuals with FAP is 16 years, and colonoscopy screenings are recommended to begin in these individuals either at 10 to 12 years of age or 10 years earlier than the earliest CRC diagnosis in the family, whichever comes first.

Assessing CRC risk in younger adults may not only result in earlier screening among high-risk young individuals but may also increase screening rates of average-risk individuals when they reach 50 years of age by introducing the concept of CRC screening earlier. Proactively identifying individuals with a family history or other predisposing factor, such as inflammatory bowel disease or a relevant hereditary syndrome (accounting for 6% of CRC cases), may also lead to recommending risk modification (eg, weight reduction, increased exercise, smoking cessation, and correction of vitamin D deficiency) or considering prophylactic surgery in certain cases.

### EVALUATION OF COLORECTAL SYMPTOMS IN YOUNG INDIVIDUALS

Screening is relevant only for asymptomatic individuals. Once CRC symptoms arise, however, an expeditious work-up is essential for all patients. Unfortunately, lack of awareness of the increasing

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<th>TABLE 2. Family History and Individual Risk for Colorectal Cancer (CRC)</th>
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<td>Family history</td>
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<tr>
<td>No history of CRC or adenoma (%)</td>
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<tr>
<td>One second-degree or third-degree relative with CRC</td>
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<td>One first-degree relative with an advanced adenomatous polyp</td>
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<td>One first-degree relative with colon cancer</td>
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<td>Two second-degree relatives with colon cancer</td>
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<tr>
<td>Two first-degree relatives with colon cancer</td>
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<tr>
<td>First-degree relative with CRC diagnosed at &lt;50 y</td>
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*Second-degree relatives include grandparents, grandchildren, aunts, and uncles.
*Third-degree relatives include great-grandparents and cousins.
*First-degree relatives include parents, siblings, and children.

Adapted from National Colorectal Cancer Roundtable, with permission.

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<th>TABLE 3. Risk Classification</th>
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<td>Average risk</td>
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<td>Increased risk</td>
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<td>High-risk familial syndromes</td>
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CRC = colorectal cancer; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer.

Adapted from National Colorectal Cancer Roundtable, with permission.
incidence of young-onset CRC and, consequently, a low suspicion of cancer may delay the thorough symptom evaluation needed to effectively establish or rule out young-onset CRC. Patients with young-onset CRC and their physicians both appear to contribute to delayed diagnosis. On average, symptomatic young patients may wait approximately 6 months before seeking medical care. The decision to seek care is a complex one, and lack of knowledge about the disease, lack of recognition of the potential seriousness of symptoms, embarrassment about and denial of symptoms, and limited social networks or support may all contribute to patient-mediated delays in symptom evaluation for all age groups. In adolescents and young adults, psychological factors (eg, sense of invincibility) and lack of insurance may also delay seeking care. Once young patients present with colorectal symptoms, they may also encounter physician-related delays (eg, missed symptoms and initial misdiagnosis), which occur in 15% to 50% of young-onset CRC cases.

By discussing CRC risk factors and symptoms, the importance of screening, and the value of early detection during routine visits, PCPs may help young patients be alert to symptoms and seek care earlier. Given the limited time for PCP-patient interactions, a team approach drawing on the expertise of physician assistants, nursing staff, and health educators may provide an effective way to educate young patients about CRC.

In addition, PCPs can further reduce the risk of delayed or missed diagnoses by considering CRC as a real possibility in young patients who present with a suggestive family history and/or any of the common CRC symptoms (ie, rectal bleeding, abdominal pain, change in bowel habits, and anemia), which occur in 15% to 50% of young-onset CRC cases.

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The rate of CRC among men and women with rectal bleeding is approximately 25 times that of the general population. A change in bowel habits is somewhat more indicative of CRC in men than in women. Anemia is also more predictive of CRC in men than in women because a number of other conditions may cause anemia in women. Although the rate ratios vary by symptom and for men and women, these data clearly underscore the importance of careful and timely symptom evaluation. The presence of a second symptom doubles the absolute risk of CRC in individuals for all age groups combined. Rectal bleeding is a common symptom, especially in combination with anemia, and should be thoroughly investigated. Bright red blood on the surface of brown stool or on toilet tissue along with brown stool or blood dripping or squirting into the bowl, for example, may suggest a distal lesion that can often be evaluated with sigmoidoscopy alone.

Not all patients with CRC present with clear-cut colorectal symptoms. In a recent study, 86% of 1025 patients with young-onset CRC (mean age, 42.6 years for colon cancer patients and 42.2 years for rectal cancer patients) were symptomatic at diagnosis. Patients with rectal cancer were more likely to present with symptoms than those with colon cancer (90% vs 83%; P<.001). Clinical work-ups of the apparently asymptomatic patients revealed anemia (14%), positive fecal occult blood test result (7%), abdominal mass (2%), and mass on digital rectal examination (2%).

Because most young-onset CRCs occur in the rectum, rectosigmoid colon, and distal colon, sigmoidoscopy may be particularly useful in establishing or ruling out young-onset CRC and can provide initial evaluation of outlet-type rectal bleeding (eg, bright red blood appearing during or after a bowel movement). However, in individuals younger than 55 years, 30% of lesions can occur proximal to the splenic flexure and would be missed by sigmoidoscopy. Colonoscopy is recommended if no anorectal cause is apparent for outlet bleeding and if bleeding persists, regardless of the patient’s age. Cost-effectiveness data are limited, but at least one study has reported colonoscopy to be cost-effective in evaluating individuals 25 to 45 years of age with rectal bleeding and no other symptoms.

SHOULD AVERAGE-RISK CRC SCREENING BE INITIATED EARLIER?

Population-based CRC screening for asymptomatic, average-risk individuals starting at 50 years of age is supported by the US Preventive Services Task Force, the Agency for Healthcare Policy and Research, the US Multi-Society Task Force, and various specialty organizations. From 1975 to 2000, screening has been credited with approximately half of the 22% decrease in
CRC incidence and the 26% reduction in CRC mortality, with treatment and risk factor reductions accounting for the remaining gains.5

Because CRC risk varies somewhat by race and sex, subgroups of the average-risk population may benefit from different screening schedules. Research estimating that 10.9% of African Americans had CRC diagnosed before 50 years of age informed the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy recommendations for African Americans to begin screening at 45 years of age.47,68

However, evidence is currently insufficient to justify initiation of population-wide CRC screening among asymptomatic, average-risk patients who are younger than 50 years. Some researchers have suggested that average-risk screening might begin at the age of 40 years because the CRC incidence rate at the age of 40 years is similar to the cervical cancer rate because the CRC incidence rate at the age of 40 years is similar to the cervical cancer rate that prompted the adoption of routine screening with Pap smears.19 The presumed benefits that earlier screening offers to these younger individuals would include better outcomes stemming from early detection and even cancer prevention through the detection and removal of polyps at the precancerous stage. On the other hand, decision analysis models have not identified substantial life-year gains for initiation of average-risk screening at the age of 40 years, in part because the overall adenoma prevalence at the age of 40 years is low, and there is not yet robust evidence of a more rapid adenoma-carcinoma sequence in younger individuals.57 Therefore, currently, the US Preventive Services Task Force and the US Multi-Society Task Force have deemed the current scientific evidence insufficient to justify this large-scale policy change.47,69 There is also concern that making CRC screening recommendations more complex could be a barrier to increasing overall screening rates.45,64

CONCLUSION
In the United States, CRC incidence and mortality are increasing at a significant rate each year in men and women younger than 50 years and steadily decreasing in all other age groups. Primary care physicians can play a critical role in decreasing the incidence and mortality of young-onset CRCs by changing their approach to evaluating and educating their younger patients. Primary care physicians can use readily available tools to obtain a detailed family history, taken well before the age of 50 years, to assess each patient’s CRC risk and then recommend earlier screening to those who meet high-risk family or personal history criteria. Through referrals, genetic counselors can assess patients with suspected high-risk hereditary syndromes, and patients with a confirmed hereditary syndrome can be directed to appropriate screening protocols, prophylactic operations, and/or other risk modification strategies. In addition, PCPs have an important and immediate opportunity to improve detection of CRC in younger patients by maintaining awareness that CRC most often occurs in individuals with no family history or apparent risk factors and is increasingly occurring in individuals younger than 50 years. Young-onset CRC often presents at advanced stages in part due to patient-mediated delays and missed symptoms and misdiagnosis or delays in diagnosis by the physician. Referrals for sigmoidoscopy and colonoscopy should be used as appropriate for patients who present with unexplained persistent rectal bleeding, iron deficiency anemia, or recent and persistent alterations in bowel habits. Clinical studies are needed to estimate the potential decreases in young-onset CRC incidence and mortality from improved screening use in high-risk individuals and more effective diagnostic work-ups in younger symptomatic individuals. In the meantime, discussions of lowering the CRC screening age for some segments of the average-risk population are under way.

Abbreviations and Acronyms: APC = annual percent change; CRC = colorectal cancer; FAP = familial adenomatous polyposis; FDR = first-degree relative; HR = hazard ratio; MSS = microsatellite stable; PCP = primary care physician; SEER = Surveillance, Epidemiology, and End Results

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