REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Increasing Incidence of Early-Onset Colorectal Cancer

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Colorectal cancer is the third most common cancer worldwide and the second most common cause of cancer-related death.[1] An alarming increase in cases of early-onset colorectal cancer, defined as diagnosis in patients younger than 50 years of age, has occurred in the United States and other high-income countries over the past few decades (Fig. 1).[2,3] Early-onset colorectal cancer now accounts for approximately 10% of all new diagnoses of this cancer,[5] and an accompanying increase in colorectal cancer–related mortality during the past decade has also been observed among younger patients.[6,7] This trend is in sharp contrast to the steady decline in the incidence of later-onset colorectal cancer and related mortality over the past two decades in the United States (Fig. 1) and other high-income countries,[8] which is attributed primarily to screening and to a lesser extent to surveillance and treatment. The concurrent increase in early-onset colorectal cancer and decline in later-onset cases have shifted the median age at diagnosis from 72 years in the early 2000s to 66 years at present.[7] In the next 10 years, it is estimated that 25% of rectal cancers and 10 to 12% of colon cancers will be diagnosed in persons younger than 50 years of age.[5,8]

Although patients with early-onset colorectal cancer are more likely to have a hereditary syndrome than those who have later-onset disease, most cases are sporadic, with no identifiable cause. Furthermore, somatic mutational profiling of early-onset colorectal cancers has not revealed previously unidentified or actionable alterations to inform our understanding of the pathogenesis of these cancers or to guide treatment. In this review, I discuss current evidence regarding phenotype and diagnosis of early-onset colorectal cancer, as well as strategies to address the increasing incidence of this disease.

CLINICAL PHENOTYPE

Clinical features of early-onset colorectal cancer differ from those of later-onset disease. Early-onset colorectal cancers are most commonly detected in the rectum, followed by the distal colon; more than 70% of early-onset colorectal cancers are in the left colon at presentation.[9-12] By comparison, later-onset colorectal cancers (those diagnosed in patients ≥50 years of age) occur at similar frequencies in the proximal colon and distal colorectum. Overall, colorectal cancer rates are 30% higher among men than among women; however, the difference in rates between sexes is more pronounced for rectal cancer than for colon cancer.

Early studies, including analyses of the Surveillance, Epidemiology, and End Results (SEER) database, suggested higher rates of poorly differentiated cancers and those with signet-ring cells among patients with early-onset colorectal cancer (particularly among patients <40 years of age) than among patients with later-onset disease.[11,13-15] However, many of these studies lacked data on high-frequency

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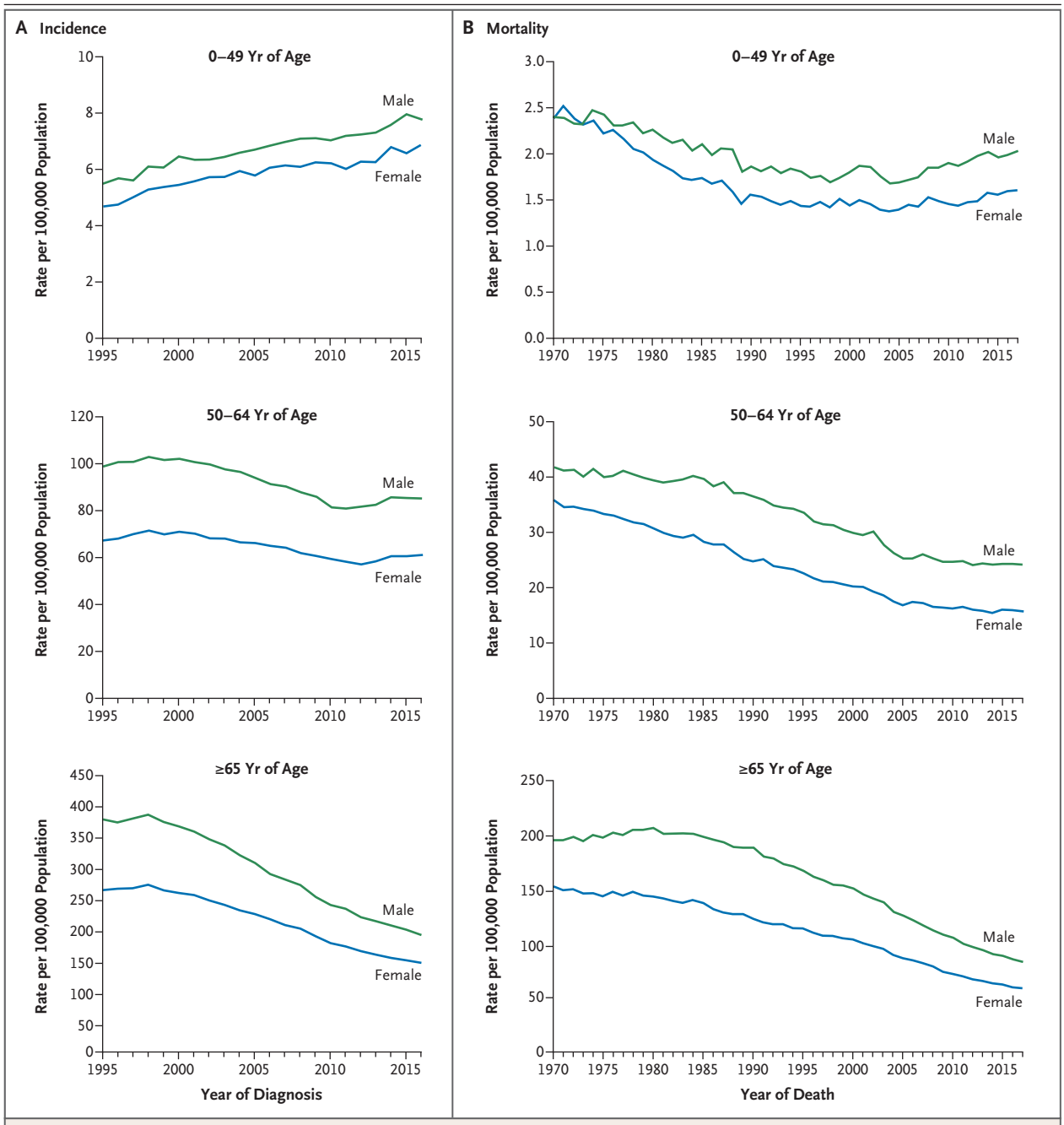

Figure 1. Trends in Colorectal Cancer Incidence (1995–2016) and Mortality (1970–2017) in the United States, According to Age and Sex. Incidence (Panel A) and mortality (Panel B) are age-adjusted to the 2000 U.S. population. Data are from the North American Association of Central Cancer Registries (2019), the National Center for Health Statistics (2019), and the American Cancer Society, Surveillance Research (2020).[4]

microsatellite instability (MSI-H), which is a consequence of deficient DNA mismatch repair (dMMR) that results in hypermutation. More recent reports indicate that early-onset colorectal cancers are more likely than later-onset cancers to display MSI-H, which is strongly associated with poor tumor differentiation.[16] In a study involving 759 patients with early-onset colorectal

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cancer who were seen at the Memorial Sloan Kettering Cancer Center between 2014 and 2019, with cases involving MSI-H or a known clinical or hereditary predisposition to colorectal cancer excluded, no significant differences in tumor grade or genomic tumor profiles were seen between patients with early-onset and those with later-onset colorectal cancer.[10] In patients with early-onset colorectal cancer, MSI-H tumors are more commonly due to germline mutations in MMR genes[17-19] than to epigenetic inactivation of the *MLH1* MMR gene, which is more common in sporadic MSI-H tumors seen in patients with later-onset colorectal cancers.[20,21]

A more advanced TNM (tumor–node–metastasis) stage of disease (i.e., stage III or IV) at diagnosis is more likely in patients with early-onset colorectal cancer than in patients who have later-onset disease,[15,22,23] as shown in studies that included large, population-based cohorts.[23-25] This finding raises the question of whether the advanced stage of early-onset tumors represents a more aggressive tumor biology or a delayed diagnosis; the finding may also reflect, in part, a reduction in the stage at diagnosis in patients 50 years of age or older due to screening. Presentation with a more advanced stage of disease may well be due to the observation that patients with early-onset colorectal cancer have had a longer duration of symptoms at presentation and a longer delay in the time to diagnosis (7 to 9 months) than older patients.[22,26,27] A symptomatic presentation of colorectal cancer is associated with a more advanced stage of disease, which in turn is associated with a poor prognosis. In a single-center study of a large cohort of patients with early-onset colorectal cancer, the most common symptoms at presentation were hematochezia (in 38% of the patients), abdominal or pelvic pain and bloating (in 33%), and a change in bowel habits (in 20%).[10] These symptoms are more common with tumors of the rectum and left colon, which typify early-onset colorectal cancers.

Patients with early-onset colorectal cancers are often unaware of this disease and its symptoms, which are frequently attributed to common, benign conditions.[28] Patients under the age of 50 years, especially men, are less likely than older patients to have a primary care provider, to seek primary care, and to be insured. Health care providers may also be more likely to defer or forgo testing in younger than in older symptomatic patients.[29,30] There is a need for increased awareness of this cancer on the part of both younger patients and their health care providers. In addition, physicians should be mindful of the burden of this disease with respect to treatment-related side effects, including sexual dysfunction, infertility, and financial and psychosocial consequences.

EPIDEMIOLOGY

In the United States, the age-adjusted incidence of early-onset colorectal cancer rose from 7.9 to 12.9 cases per 100,000 people between 1988 and 2015, a 63% increase.[9] The steady rise in the incidence of early-onset colorectal cancer has occurred throughout the developed world, which suggests that similar risk factors and exposures within these geographic areas are major contributors. A marked increase has been seen among non-Hispanic White persons, whereas the incidence has been relatively stable, yet elevated, among Black persons.[2,31] The explanation for the rapid increase in incidence among White persons is unknown. Exposures would have to occur early in life to account for early-onset colorectal cancer. Putative risk factors identified in case–control studies overlap with established risk factors for later-onset disease.

A change in diet began about 50 years ago that involved an increased consumption of red and processed meat,[32,33] as well as refined grains and processed sugar.[33-35] Modifiable risk factors, ranked on the basis of relative risk data from highest to lowest, include a Western dietary pattern, smoking (current vs. never), consumption of red and processed meat, and overweight and obese body habitus.[32-34,36] In the Nurses' Health Study II (1991–2015), a Western-style diet was associated with an increased risk of early-onset, high-risk colorectal adenomas (established precursor lesions of colorectal cancer), particularly in the distal colon and rectum.[37] In contrast to refined grains, whole grains have been shown to provide protection against colorectal cancer, whereas the protective effect of fruits and vegetables has been relatively weak and inconsistent.[33,34] Consumption of sugar-sweetened beverages is highest among adolescents and young adults. In the Nurses' Health Study II, women who consumed

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two or more daily servings of sugar-sweetened beverages in adulthood had a risk of early-onset colorectal cancer that was increased by a factor of 2, as compared with women who consumed less than one serving per week.[38] Furthermore, each increment in the number of servings per day from the age of 13 to 18 years was associated with a 32% increased risk of early-onset colorectal cancer.

Increased physical activity has been shown to reduce the risk of colorectal cancer,[39] whereas sedentary behavior is associated with an increased risk of early-onset colorectal cancer.[40] The prevalence of obesity among adults in the United States rose from 30.5% in 1999 to 42.4% in 2017, and the prevalence of severe obesity nearly doubled during that interval.[41] Data from an observational study[41] and a prospective cohort study[42] showed that obesity in adolescence was associated with an increased incidence of early-onset colorectal cancer and related mortality. Obesity was also found to be significantly associated with early-onset colorectal cancer in a nested case–control study among members of the Kaiser Permanente Southern California health plan.[43] However, other case–control studies have shown conflicting results.[44] Only limited data from prospective studies have identified obesity as a risk factor.[45]

A potential for reverse causality complicates these studies, since body weight is measured at study entry and does not account for potential disease-related weight loss before the diagnosis of colorectal cancer. Furthermore, abdominal fat may be more important than overall body weight in influencing risk.[46] The prevalence of metabolic syndrome has increased among young adults and is associated with early-onset colorectal cancer.[47] Type 2 diabetes mellitus has increased substantially among younger adults. Although inconsistent results have been reported,[48] patients with adult-onset type 2 diabetes have a slightly increased risk of colorectal cancer (which is stronger for men than for women),[49] even when the analysis accounts for risk factors, including physical activity, body-mass index, and waist circumference.[50]

Although a primary or predominant risk factor accounting for the worldwide increase in early-onset colorectal cancer has not been found, a multifactorial risk profile is probably responsible, including lifestyle and environmental exposures over several decades that can alter the gut microbiome (Fig. 2). Abundant evidence links the gut microbiome with the development of colorectal cancer.[51] Gut microbes interact with the host immune system and can influence the antitumor immune response.[51] Patients with colorectal cancer have reduced bacterial diversity, as compared with healthy persons, and studies indicate that Firmicutes, Bacteroidetes, enterotoxigenic *Bacteroides fragilis*, and the oral anaerobe *Fusobacterium nucleatum* are enriched in colorectal cancer.[51,52] In addition, age-related differences in gut microbial composition have been reported among patients with colorectal cancer and dysbiosis,[53] an observation in both patients with early-onset disease and those with later-onset disease, but further studies are needed to confirm these differences.[54]

Diet influences the composition of the gut microbiome, and a Western-style diet and obesity can lead to gut dysbiosis and chronic intestinal inflammation, which can promote colorectal tumorigenesis (Fig. 2).[35,55,56] Colorectal cancer is associated with reductions in gut bacteria that produce short-chain fatty acids, which preserve intestinal immune homeostasis.[56] A plant-based diet promotes beneficial gut microbes that are antiinflammatory, whereas a Western-style diet promotes unfavorable microbes, contributing to mucosal inflammation and an increased risk of colorectal neoplasia.[57]

Analysis of data from three prospective cohort studies showed that a Western-style diet was associated with an excess of sulfur-metabolizing bacteria in feces. Patients with an excess of sulfur-metabolizing bacteria had an increased risk of colorectal cancer, after adjustment for other risk factors.[58] When assessed according to the anatomical subsite, the diet promoting sulfur-metabolizing bacteria was positively associated with distal but not proximal colon cancers. Mechanistically, sulfur-metabolizing bacteria produce hydrogen sulfide, which is genotoxic, leading to inflammation and DNA damage and thus promoting cancer.[59] In addition to the effects of diet and lifestyle on the microbiome, gut microbes mediate the effect of diet and can influence host metabolism, with immune, genetic, and epigenetic consequences. Antibiotics are known to substantially alter the gut microbiome, and prolonged use of these agents may be a risk factor for early-onset colorectal cancer.[60-62]

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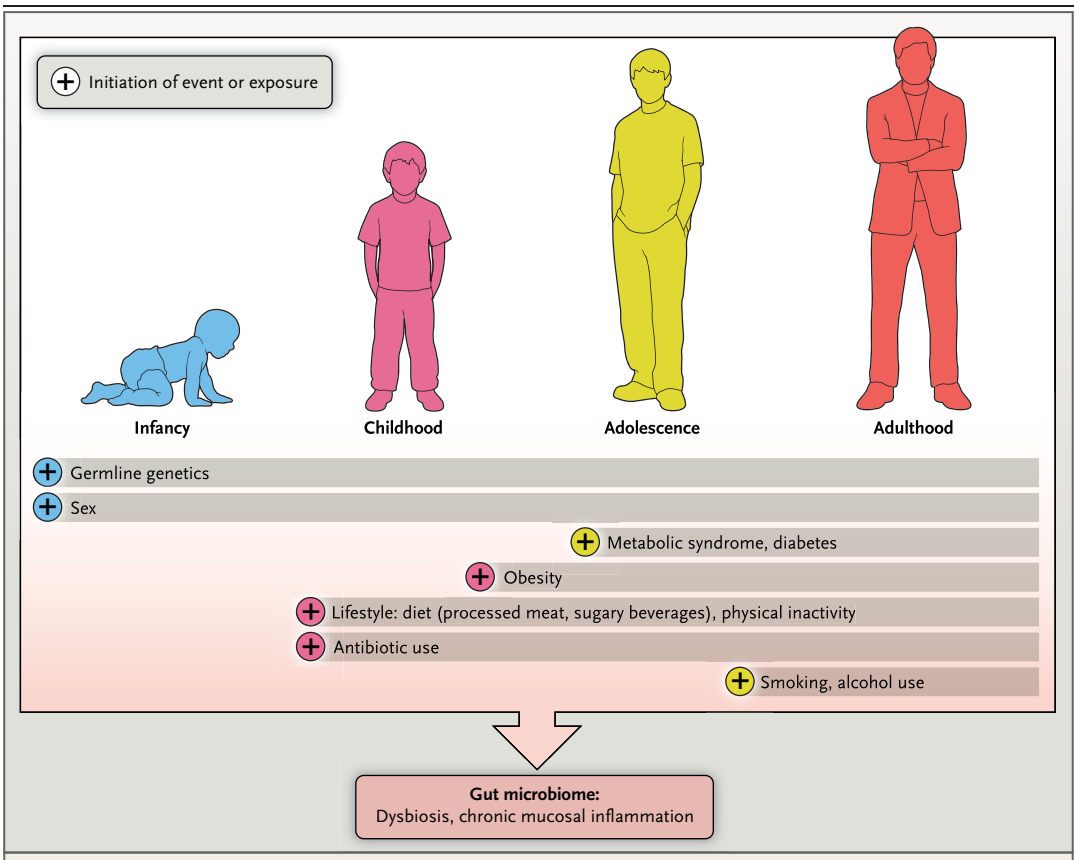

Figure 2. Factors Influencing the Risk of Colorectal Cancer.
Germline genetics, sex, diet and other lifestyle exposures, and health conditions interact with the gut microbiome over a patient's lifetime and influence the risk of colorectal cancer.

Early-life exposures warrant investigation as potential risk factors for early-onset colorectal cancer. Data from large, prospective cohort studies can allow for an examination of early-life exposures in relation to cancer risk. The ongoing Nurses' Health Study 3 includes 45,000 U.S. nurses (≥18 years of age) and has an accrual goal of 100,000 participants. The effect of diet, lifestyle, and environmental exposures on the risk of early-onset colorectal cancer will be examined from adolescence to adulthood. The Colon Cancer Family Registry Cohort study is also collecting information, including risk factors, from patients who have received a diagnosis of colorectal cancer and their family members. The second phase of recruitment includes biospecimen collection.[63] European investigators have initiated the Colorectal Cancer Pooling Project, which will pool data from more than 25 prospective cohort studies to analyze potential risk factors and biomarkers across age groups of patients with colorectal cancer.

GENETIC TESTING

Nearly 30% of patients with early-onset colorectal cancer have a family history of this cancer in at least one first-degree relative.[19] Population-based data indicate a 3 to 5% overall prevalence of hereditary colorectal cancers, of which the Lynch syndrome is the most common.[64] The Lynch syndrome is undiagnosed in the majority of affected patients, who are unaware that they are at high risk for cancer. The syndrome is due to a germline mutation in an MMR gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) that results in dMMR and MSI-H. Current guidelines recommend universal testing of all newly diagnosed colorectal cancers for MMR and MSI status in order to detect the Lynch syndrome.[65] Such test-

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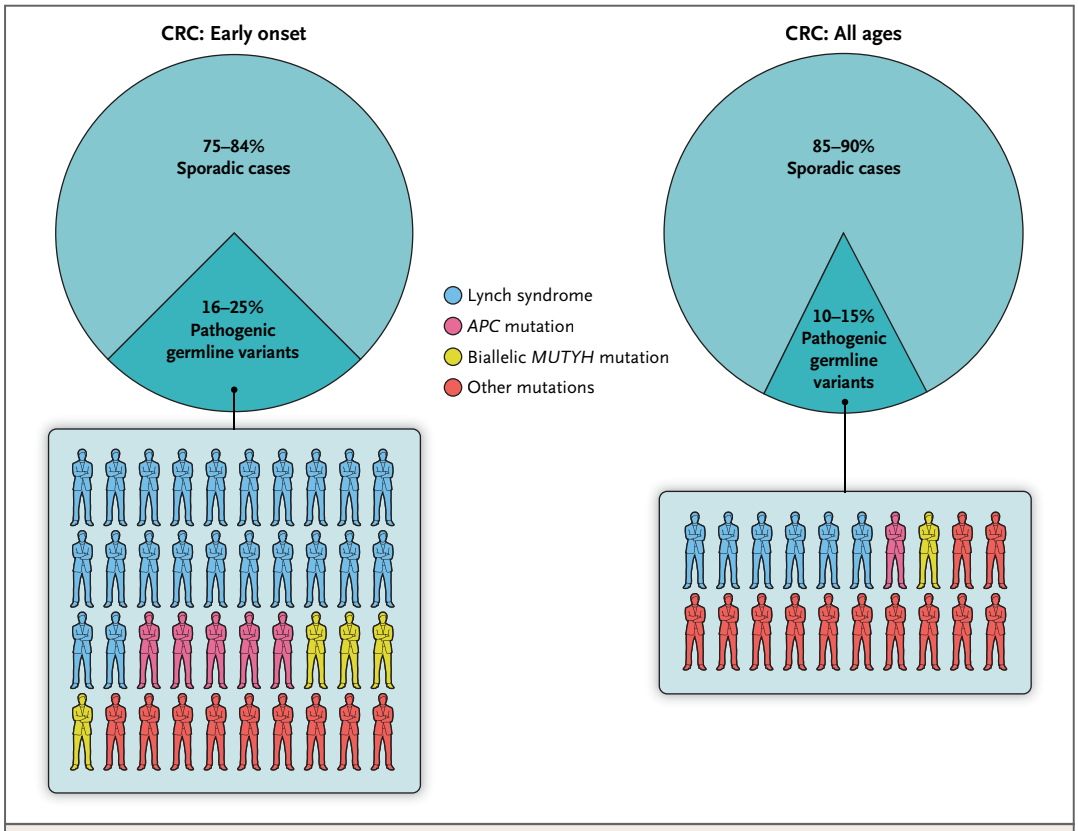

Figure 3. Prevalence of Pathogenic Germline Variants in Patients with Early-Onset Colorectal Cancer (CRC).
The prevalence of pathogenic germline variants is shown for early-onset CRC (left) as compared with CRC in all age groups (right).[18,19,67,68] Germline variants in the high-penetrance genes *APC* and *MUTYH* cause colonic polyposis syndromes.

ing is also of therapeutic importance in patients with metastatic colorectal cancer, since those with dMMR or MSI-H are candidates for first-line treatment with an immune checkpoint inhibitor.[66] However, the majority of early-onset colorectal cancers are sporadic and not attributable to germline mutations in cancer risk genes.

The prevalence of a mutation in a high-penetrance cancer-susceptibility gene is relatively high among patients younger than 50 years of age (Fig. 3). Germline multigene panel testing has shown that the prevalence of pathogenic germline variants in patients with early-onset colorectal cancer (16 to 25%) is nearly double the prevalence in unselected patients with colorectal cancer.[17-19,69] In a study that prospectively identified 450 patients with early-onset colorectal cancer at 51 hospitals in Ohio, multigene panel testing (25 genes) identified germline mutations in 16% of patients, approximately half of whom had the Lynch syndrome.[18] One third of the patients who had mutations did not meet guideline-based genetic testing criteria for the mutated gene. In a study at a tertiary care clinic, 315 patients under the age of 50 years who had received a diagnosis of colorectal cancer underwent clinical germline sequencing; 25% of the patients had a hereditary colorectal cancer syndrome.[19]

Some tumors display dMMR or MSI-H, but no germline mutation can be identified. Tumor sequencing is useful in these so-called Lynch-like tumors, since many of these cases have double somatic MMR mutations or a somatic mutation with loss of heterozygosity of the other allele.[18,70,71] A study involving 759 patients with early-onset colorectal cancer showed a 17.5% prevalence of pathogenic germline variants.[10] In this cohort, mutations in MMR genes conferring the Lynch syndrome were most common and

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Key Points Related to Early-Onset Colorectal Cancer

- Early-onset colorectal cancer (diagnosed in patients <50 years of age) accounts for 10% of new cases of colorectal cancer; the incidence has been steadily increasing in high-income countries since 1988.
- The majority of patients present with cancers in the left colon; a more advanced stage of disease at diagnosis is more likely than in patients with later-onset colorectal cancer.
- Multiple risk factors have been proposed, including a Western-style diet, which can alter the gut microbiome and may lead to gut inflammation and an increased risk of colorectal cancer.
- Pathogenic germline variants are present in one in six patients, and half of these variants are in mismatch repair genes associated with the Lynch syndrome.
- The National Comprehensive Cancer Network recommends genetic risk counseling and evaluation for all persons who have received a diagnosis of early-onset colorectal cancer; the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer recommends germline multigene panel testing in all patients with colorectal cancer who are under the age of 50 years.
- The American Cancer Society recommends starting colorectal cancer screening at the age of 45 years for persons at average risk for early-onset or later-onset disease.

were detected overall in 5.5% of the patients. In a study involving 1058 patients with colorectal cancer who were treated at the Dana–Farber Cancer Institute, germline panel testing (25 genes) without preselection for age, family history, or MSI status showed that 9.9% of the patients had one or more pathogenic variants, and 31.4% of the patients with pathogenic variants had the Lynch syndrome.[69] The median age at first diagnosis was 56 years, and 31.8% of the patients had early-onset colorectal cancer. In the subgroup of patients with early-onset disease, 14.0% had at least one germline variant, and 44.7% of those patients had the Lynch syndrome. Taken together, these studies show the presence of pathogenic germline variants in approximately one in six patients with early-onset colorectal cancer, and half of these variants are in MMR genes associated with the Lynch syndrome (see text box).

Only half of patients found to have a pathogenic germline variant report a family history of colorectal cancer in a first-degree relative.[19] Given this finding and the limited sensitivity of clinical criteria, the position statement of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer recommends genetic testing by means of next-generation sequencing with the use of a germline multigene panel in all patients with colorectal cancer who are under the age of 50 years.[72] Similarly, the National Comprehensive Cancer Network recommends genetic risk counseling and evaluation for all persons with early-onset colorectal cancer.[65] Germline panel testing by means of next-generation sequencing should include, at minimum, the MMR genes, as well as six genes that account for a smaller overall fraction of incident colorectal cancer but are nonetheless associated with an elevated risk of cancer in carriers (*APC*, *MUTYH*, *BMPR1A*, *SMAD4*, *PTEN*, and *STK11*). These six genes cause various forms of polyposis.[72] With the increasing use of multigene panel testing, more Lynch mutations are being recognized in persons who do not fulfill clinical criteria for the diagnosis of this syndrome. Less common than the Lynch syndrome are hereditary colonic polyposis syndromes, of which familial adenomatous polyposis, due to a germline mutation in *APC*, is the most prevalent, and *MUTYH*-associated polyposis, caused by biallelic *MUTYH* pathogenic variants, is also associated with an increased risk of colorectal cancer (Fig. 3).[18,19,65,67,68]

Genetic counseling enables discussion of genetic testing and its results, including the potentially limited clinical usefulness of identifying a pathogenic variant in genes of moderate penetrance. Counseling also encompasses discussion of insurance coverage, protection from genetic discrimination, psychosocial concerns, and implications for family members of patients found to have a pathogenic variant, since cascade testing of at-risk relatives can prevent new cancer diagnoses.

MOLECULAR PHENOTYPE

Colorectal cancers are molecularly heterogeneous tumors, and although alterations have been shown to be relatively similar across age groups, some differences have been identified. Among early-onset colorectal cancers, the frequency of MSI-H was 17.0% in a population-based series of patients,[73] and a range of 8.1 to 26.0% has been reported in clinic-based cohorts.[17-19,69] Most MSI-H colorectal cancers in younger patients are due to the Lynch syndrome, whereas later-onset colorectal cancers are enriched with sporadic MSI-H tumors due to *MLH1*

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hypermethylation and frequent *BRAF* V600E mutations.[20,21]

In a study of 18,218 colorectal cancer cases that were analyzed with the use of a next-generation sequencing panel with 403 cancer-related genes, genomic alterations were compared among patients divided into three age groups: younger than 40 years, 40 to 49 years, and 50 years or older.[74] Molecular alterations in microsatellite-stable (MSS) cancers were similar across age groups, except that *APC*, *KRAS*, and *BRAF* mutations were significantly more common in patients 50 years of age or older and alterations in *TP53* and *CTNNB1* (the latter encoding β-catenin) were more common in patients younger than 40 years of age.[74] In a single-institution study that categorized patients by age, somatic mutational profiles in MSS colorectal cancers were found to be indistinguishable between patients with early-onset colorectal cancer (759 patients) and those with later-onset colorectal cancer (687 patients), including driver pathway gene alterations.[10] Furthermore, no significant differences in tumor mutational burden, the fraction of the genome altered, or loss of heterozygosity were found between early-onset and later-onset colorectal cancers.[10]

Cancer risk is influenced by polygenic effects, in addition to single-gene alterations and gene–environment interactions. In an international consortium analysis of data from case–control and cohort studies, with a total of more than 50,000 patients with colorectal cancer, more than 12,000 of whom had early-onset disease, a polygenic risk score was determined on the basis of 95 genomewide single-nucleotide polymorphisms. Patients with scores in the highest quartile had a risk of early-onset colorectal cancer that was increased by a factor of 3.7, as compared with patients who had scores in the lowest quartile,[75] and the risk score was more informative for early-onset colorectal cancer than for later-onset disease, particularly in the absence of a family history of this cancer.

PROGNOSIS

Patients with early-onset colorectal cancer tend to present with advanced-stage disease, which is associated with increased mortality. Younger patients are more likely to receive postoperative (i.e., adjuvant) chemotherapy and multiagent regimens.[23] In pooled data from patients with stage II or stage III colon cancer treated in six recent clinical trials of adjuvant chemotherapy, survival was similar for patients with early-onset disease and those with later-onset disease.[76] Patients with early-onset colorectal cancer had more metastatic regional lymph nodes but were significantly more likely to complete the planned treatment and to receive it at a high dose intensity. In another study reporting pooled data from 25 randomized trials involving patients with stage III colon cancer, no significant difference in survival was observed in patients with early-onset disease as compared with later-onset disease after adjustment for MMR genes, *KRAS*, and *BRAF* V600E.[77] Finally, a large clinical trial[78] and a single-institution study[10] showed no significant difference in survival between patients with metastatic early-onset colorectal cancer and those with metastatic later-onset disease. Taken together, these data suggest that worse outcomes for patients with early-onset colorectal cancer appear to be due primarily to more advanced disease at diagnosis.

SCREENING

Early detection of the disease can substantially reduce mortality. Despite the established benefits of colorectal cancer screening in persons who are 50 years of age or older, only 68.8% of eligible persons in the United States undergo such screening.[79] Barriers include lack of knowledge of the benefits of screening, lack of access to a health care provider or recommendations for screening, and reluctance to undergo screening. The rate of screening is lower among underinsured persons, those with low incomes, and racial and ethnic minorities.[79,80]

There are multiple screening options for patients at average risk for colorectal cancer, including a fecal immunohistochemical test (FIT), multitarget stool DNA testing, colonoscopy, sigmoidoscopy alone or combined with FIT, and a guaiac test.[81,82] The most invasive option, colonoscopy, remains the standard for colorectal cancer screening, and has the added benefit of removal of precancerous polyps. A shared decision-making approach is advocated to select the screening test that the patient is most likely to undergo.

Until recently, the recommended age at first

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screening for persons at average risk for colorectal cancer has been 50 years in the United States and most other countries. Given the rising incidence of colorectal cancer in younger adults, the U.S. Preventive Services Task Force updated its 2016 recommendations and now concludes with moderate certainty that colorectal cancer screening in adults who are 45 to 49 years old has a modest net benefit, as compared with a substantial net benefit for those who are 50 to 75 years old.[82] Similarly, in 2018, the American Cancer Society (ACS) lowered the recommended age to begin colorectal cancer screening from 50 years to 45 years,[83,84] on the basis of modeling data suggesting that beginning screening at the age of 45 years was associated with a higher number of predicted life-years gained and an improved balance between screening burden and benefit.[83-85] Furthermore, the ACS task force considered empirical data from the SEER database that suggest that initiating screening at 45 years of age would prevent more early deaths than starting to screen at 50 years of age.[84] However, studies confirming the effectiveness of colorectal cancer screening in persons between the ages of 45 and 49 years have not been conducted.

Lowering the age at which screening begins has been controversial, given the observation that a large relative increase in cases of early-onset colorectal cancer corresponds to a smaller absolute increase in incidence.[86] Approximately half of patients with early-onset colorectal cancer receive the diagnosis at an age younger than 45 years and will be unaffected by lowering the age at initial screening. Furthermore, an increase in the number of persons who undergo colorectal cancer screening will require an increase in available resources for screening and will place a greater demand on capacity for screening, which may limit access for older adults, who are more likely to benefit from screening.[83,85,87] Lowering the age when screening begins may also disproportionately affect marginalized populations, which are already less likely to undergo screening.

An individualized approach, with the initiation of colorectal cancer screening based on family history, has been recommended. With this approach, people who have a first-degree relative in whom colorectal cancer or an advanced adenoma is diagnosed before the age of 60 years, or two first-degree relatives who receive a diagnosis at any age, are advised to begin undergoing screening colonoscopy at the age of 40 years, or at an age that is 10 years younger than the age of the family member with the earliest diagnosis.[88] Among patients with early-onset colorectal cancer who are 40 to 49 years of age, 25% meet family history criteria for early screening. If earlier screening had been performed in patients who met these criteria, their cancers could have been diagnosed earlier or at a premalignant stage.[63] Other risk models for screening that use more detailed family history data, as well as genetic risk scores and lifestyle factors, are an active area of research. Regrettably, many patients lack detailed knowledge of their family history, often because of poor communication within families, and such information is frequently not elicited by physicians.

STRATEGIES TO REDUCE EARLY-ONSET COLORECTAL CANCER

The challenges and barriers to compliance with guidelines for colorectal cancer screening must be addressed for younger adults, as well as for persons at average risk who are 50 years of age or older. The most important factor for improving adherence to screening guidelines is a physician's recommendation.[89] Primary care physicians should tailor screening recommendations, including noninvasive, stool-based tests, on the basis of patients' preferences. Obtaining and updating family history data are important in the identification of patients at high risk, for whom individualized screening guidelines can be implemented. Universal testing of colorectal cancers for the Lynch syndrome is an important step forward, as is the recommendation of germline multigene panel testing for all early-onset colorectal cancers.[72] A new screening approach is the assessment of circulating tumor DNA in blood plasma for the detection of early-stage colorectal cancer.[90] If this approach is found to be successful in clinical trials, it has the potential to increase screening rates.

Issues of access to care must be addressed; many young persons, especially men, lack a primary care provider. Educational campaigns are needed to increase public awareness of early-onset colorectal cancer and to inform primary care providers about the rising incidence of early-onset cases. Experience has shown that a celeb-

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rity spokesperson can have a substantial effect on public awareness and participation in cancer prevention, including colon cancer screening. Ongoing prospective cohort studies will enable the examination of early-life exposures, with the potential for evaluation of biospecimens to gain mechanistic insights into carcinogenesis. Since colorectal carcinogenesis occurs over a period of more than a decade, future studies are needed to elucidate how environmental factors can influence cancer risk through modulation of gut microbial composition and function before neoplastic development.

CONCLUSIONS

The incidence of early-onset colorectal cancer is projected to steadily increase and more than double by 2030. Delayed diagnosis in younger patients and presentation with advanced disease stages underscore the need for greater awareness of the disease on the part of the general public, as well as health care providers. Patient education is a key factor in promoting the benefits of screening, overcoming barriers to screening, and increasing adherence to current screening guidelines. More tailored preventive and screening strategies based on risk profiling are needed. The focus belongs on sporadic disease, since hereditary syndromes account for up to 25% of cases of early-onset colorectal cancer, with the Lynch syndrome being the most common.

The availability of multigene panels for germline testing offers the potential to increase the detection of hereditary syndromes in clinical practice. Although the specific causes underlying the increasing incidence of early-onset colorectal cancer remain elusive, ongoing research involving large cohorts and international consortia aims to identify early-life exposures that are most relevant to the development of early-onset disease. Data suggest a considerable overlap with risk factors for later-onset colorectal cancer, including a Western-style diet, which can alter the gut microbial composition, resulting in dysbiosis and chronic inflammation. Public health measures are needed to address poor dietary habits, obesity, and physical inactivity among adolescents. A healthier diet, especially one that is plant-based, promotes a more favorable gut microbiome and may reduce the risk of colorectal cancer. We must also address the consequences of early-onset colorectal cancer, including psychosocial challenges and a reduced health-related quality of life.

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