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Alarming Recent Rises in Early-Onset Colorectal Cancer

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Because of recent increases in early-onset diagnoses, nearly 10% of colorectal cancers (CRCs) are now diagnosed in individuals younger than 50 years.[1,2] CRC is a deadly and all too commonly diagnosed cancer. For the 39% of patients with CRC fortunate enough to be diagnosed with localized-stage disease, the 5-year survival rate is 90%; however, this declines to 71% for patients with cancers that have spread regionally and is lowest at 14% for those diagnosed with distant metastases.[2] Despite important gains in CRC prevention among adults aged 50 years or older, especially since guideline recommendations for routine screening were introduced in the 1970s, the CRC risk for younger adults has been gradually rising. Increases were previously observed to be as high as 3% annually for adults aged 20 to 29 years and 0.5% to 1.3% for adults aged 40 to 50 years.[1] Early-onset CRC has also been highlighted in the media recently in light of the untimely death of celebrated Hollywood actor Chadwick Boseman, who was just 39 years old at the time of his diagnosis.[3] In 2018, the American Cancer Society lowered its recommended age for starting CRC screening from 50 to 45 years,[4] and in May 2021, the US Preventive Services Task Force followed suit.[5]

In the current issue of *Cancer*, Shah et al[6] report a comprehensive analysis of trends in early-onset CRC across all 50 states through 2017. Using sophisticated regression modeling techniques, they estimated recent annual percentage increases as high as 6.6% for persons aged 20 to 24 years and identified a temporal “inflection point” highlighting an acceleration of early-onset CRC incidence starting around 2012-2013, especially among non-Hispanic Whites (NHWs) and Hispanics. For example, the annual percentage change in NHW CRC incidence rates between 2001 and 2011 was 1.69 (95% CI, 1.20-2.18); this increased to 3.56 (95% CI, 2.68-4.45) between 2011 and 2017. Similarly, for Hispanics, the annual percentage change was 0.4 (95% CI, −0.07 to 0.87) from 2001 to 2013 and 4.87 (95% CI, 2.65- 7.14) from 2013 to 2017. Compared with previous descriptive studies of early-onset

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CRC, the current study updates our understanding of this emerging epidemic in a few important ways. First, it leverages data from the US Cancer Statistics national registry, which enumerates cancer incidence across all 50 US states by combining the National Program of Cancer Registries of the Centers for Disease Control and Prevention and the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. Second, though still hampered by systemic lags in the availability of cancer registry data, it does include 16 years' worth of trends, with incidence rates as recent as 2017. Finally, it performs stratification by important racial/ethnic populations that are known to be disproportionately affected by CRC, by geographic regions, and by detailed tumor sites and stages; this allows for the exploration of who is most affected, and hypothesis generation about what might be driving these increases to support tailored prevention strategies. The result is a more comprehensive and timely description of trends in the burden of early-onset CRC than has previously been available. For example, their state-by-state analysis revealed that states in the Southeast (eg, Mississippi, Kentucky, and Alabama) had the highest rates of early-onset CRC, but 18 states had average annual percentage changes higher than 2% for the study period, many of which are not in the Southeast (eg, California, Alaska, and Illinois). Some of these states with higher absolute rates or recently increasing trends are also dominated by rural areas and large proportions of NHW populations that may have been missed if the analysis had been restricted to Surveillance, Epidemiology, and End Results registries alone. Additionally and in contrast to previous analyses, their site-stratified analysis revealed these increases to be driven primarily by cancers of the colon rather than the rectum.

Most CRCs are still diagnosed in individuals older than 50 years. Across all ages, CRC incidence and mortality rates in the United States are highest in non-Hispanic Blacks (NHBs) and American Indians/Alaska Natives and lowest in Asians/Pacific Islanders (APIs).[2] From 2012 to 2016, CRC incidence rates in NHBs were 20% higher than those in NHWs and 50% higher than those in APIs, and mortality rates in NHBs were 40% higher than those in NHWs and 50% higher than those in APIs.[2] The trends noted by Shah et al[6] in early-onset CRC reflect these patterns for American Indians/Alaska Natives but not for NHBs. They also suggest that early-onset CRC may disproportionately affect NHW and Hispanic Americans. As for NHWs, these findings echo recent emerging patterns of premature death rates among NHWs living in lower socioeconomic communities outside larger urban areas.[7] Among Hispanics, these increases may be especially pronounced in states with high proportions of US Hispanics such as Texas and California, many of whom live in communities exposed to adverse underlying social and economic factors. As the field moves toward uncovering the factors driving the increased incidence of early-onset CRC, efforts must be made to ensure the inclusion of racially, ethnically, and socioeconomically diverse populations to better understand and reduce these disparities.

Because Shah et al[6] (and others before them) have observed that adults diagnosed with early-onset CRC are more likely to present with distinct histopathological and molecular features, there is growing interest in understanding the etiology of early-onset CRC and whether this etiology differs from that of CRC diagnosed among older adults or is due to an increasing prevalence of or earlier exposure to established CRC risk factors, including genetic, behavioral, and lifestyle factors.[8,9] Because early-onset CRC remains relatively

rare, few studies have examined these established risk factors for CRC in relation to early-onset disease. However, the same biological mechanisms that operate in CRC, such as insulin resistance, chronic inflammation, oxidative stress, and alterations in gut microbial composition and diversity, are hypothesized to also increase the risk of early-onset CRC. The limited existing case-control and longitudinal studies have reported increases in early-onset CRC risk associated with age and male sex[10]; a family history of CRC, alcohol intake, and consumption of processed meats[11]; and metabolic syndrome and metabolic conditions.[12] In the Nurses' Health Study II, increased sedentary television viewing time[13] and overweight/obesity and weight gain over adulthood[14] were reported to increase the risk of early-onset CRC. Encouragingly, pooling efforts, including a recently published analysis of 3 large consortia with 3767 early-onset CRC cases,[15] are underway that will help in elucidating the causes of early-onset CRC. Clearly, much more remains to be done before we fully understand the etiology of early-onset CRC.

Cancer in young adults is occurring with increasing frequency, but the reasons for this uptick in incidence are still unclear. Representative descriptive studies such as this one by Shah et al[6] provide a helpful "macro-epidemiologic" view with clues to understanding an emerging mystery. The obesity pandemic, which has accelerated among younger adults in the past 20 years, may be to blame. From 1999-2000 through 2017-2018, the prevalence of obesity in the United States increased from 30.5% to 42.4%, and the prevalence of severe obesity increased from 4.7% to 9.2%.[16] Excess body weight is associated with increased cancer risk, and higher rates of CRC incidence in the Southeast United States reflect underlying patterns of obesity in that region. Indeed, America's considerable progress toward reducing the burden of cancer at the population level may be slowing because of our food addictions and inactive lifestyles.[17] Animal models have shown that obesity not only increases cancer risk but also accelerates its development, and this could partially explain the downward shift in the age of onset for CRC.[18] Interestingly, however, although Southeastern states had the highest absolute rates of early-onset CRC and the highest underlying prevalence rates of obesity in the nation, Shah et al identified states in the West, Midwest, and Northeast as those with the highest acceleration of early-onset CRC incidence in recent years. Because obesity is lower in some of these regions than the national average, this complicates the story. However, as others have noted, unhealthy eating patterns are also important predictors of disease in lean populations. Obesogenic diets, which are high in red meat and certain fats, also cause intestinal inflammation, which can be cancer-promoting even in the absence of obesity.[19] In just the last decade, evidence implicating diets high in refined carbohydrates as promoting obesity has led to the resurgence and increasing popularity of lower carbohydrate and ketogenic diets with high fat content.[20]

We are also intrigued by the identification of 2012-2013 as an inflection point for rising rates in the last decade, which could be explained by a shift in recent dietary patterns or an increase in diagnostic investigations among young adults. Western dietary patterns, characterized by higher consumption of red meats, sugary beverages, oils, and fats and lower consumption of vegetables and fruits, have become increasingly common in recent decades, especially among younger Americans.[21] The rising prevalence of inflammatory bowel conditions such as celiac disease also reflect increases in younger adult endoscopy procedures.[22,23] In a recent study that identified an association between a poor-quality diet

and an increased risk of early-onset adenomas, 29,474 females (25% of the Nurses' Health Study II cohort) had undergone at least 1 lower endoscopy procedure before reaching the age of 50 years.[24] Increased utilization of screening procedures, even when not indicated for cancer, can increase cancer incidence rates through incidental diagnosis. Incidentalomas, as they are sometimes called, can also contribute to increasing rates of cancer because of "overdiagnosis" if the indolent cancer would not have progressed in the absence of intervention.[25] Although there is a possibility that increasing use of endoscopic procedures in younger adults is contributing to the overdiagnosis of early-stage, early-onset CRC, Shah et al[6] has found that the incidence of later stage early-onset cancers has also risen, and this points to a true increase in risk rather than a detection bias.

Improving accessibility, prompt initiation at the recommended starting age, and regular attendance to routine screening for CRC is critical. Very early-stage CRC often has no symptoms; this is one of the many reasons that population-based screening initiatives are so important. Endoscopies can identify precancerous lesions, which, once removed, mean that some forms of screening are also considered curative in nature. Expansions in Medicaid and coverage for preventive care under the Affordable Care Act successfully increased access to screening across underserved populations,[26] but there remain significant barriers to screening attendance, timely follow-up of abnormal results, and diagnosis and treatment. In 2020, the statewide prevalence of CRC test use ranged from just 60% to 75%,[2] and outreach campaigns have consistently failed to reach our most disadvantaged populations.[27] Although colonoscopy is the gold-standard method of screening for CRC, less invasive screening modalities such as stool-based tests are just as effective at reducing CRC mortality[28] and have the potential to reduce disparities in CRC screening, especially among socioeconomically disadvantaged groups that lack the time or resources needed for colonoscopy.

Screening is not a panacea. Fewer than 10% of polyps are estimated to progress to invasive cancer.[29] Even with the reduced screening age of 45 years, the US Preventive Services Task Force estimates that this change will prevent only 1 to 2 additional deaths per year.[5] For those who remain too young to be affected by the revised guidelines or uncompelled to begin screening at the recommended age, it is also important to promote symptom awareness, especially for priority populations, for which prevention efforts often fail.[30] Research and outreach that emphasize early diagnosis focus on identifying cancer at the earliest possible stage in patients with signs and symptoms (as opposed to cancer screening, which seeks to identify preclinical cancer or precancerous lesions) so that timely diagnosis and treatment can ensure the best possible outcomes.[31] National-level symptom awareness campaigns can be tailored to reach a broad audience and have been shown to be very effective in other Western countries. The most common symptoms of CRC are bleeding from the rectum, blood in the stool, changes in bowel habits, lower abdominal pain, decreased appetite, unintentional weight loss, and anemia. Importantly, older age is not a prerequisite for CRC, and alarm symptoms (eg, rectal bleeding) should be investigated promptly in patients of all ages.

This emerging epidemic also highlights important gaps in the availability of timely, representative evidence. Statewide registries suffer from excessively long lags in reporting

(up to 3+ years). Indeed, the alarming increases noted by Shah et al[6] from 2013 to 2017 may foreshadow a wave of early-onset CRC that may be upon us even before the data reflecting it are available. We also lack concrete population-level evidence about how patients (of all ages) arrive at their cancer diagnosis. The so-called 'route to diagnosis' (ie, screen detection, symptom-related detection, incidental detection, or emergency resection) has been shown to be an important predictor of outcomes and disparities.[32] A better characterization of diagnosis routes at the population level also has the potential to improve our understanding of the etiology of early-onset cancers, improve our calculation of epidemiologic measures, and facilitate the design of targeted care pathway interventions for improved outcomes.

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