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Editorial

EDITORIAL

Early-Onset Colorectal Cancer: The Mystery Remains

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In the United States, colorectal cancer (CRC) is the third cause of cancer diagnosis and the second leading cause of cancer death for men and women combined with a median age of 67 years (1). For decades, CRC has been touted as one of the most preventable cancers, with approximately 75%-80% of all patients diagnosed with sporadic disease, 1% inflammatory bowel disease (ulcerative colitis and Crohn's disease), less than 5% due to familial CRC, and a minority (<5%) attributable to inherited familial CRC syndromes (2). In the United States, the screening rate for CRC continues to be suboptimal with only 58%-76% of all age-appropriate individuals undergoing screening (3). For years, we have educated patients and providers on the importance of CRC screening for the average-risk patient beginning at 50 years of age and that a colonoscopy is the gold standard to prevent CRC (4). But prior well-established data did not explain why many individuals were meeting vibrant, healthy, young adults in their early 20s to 40s with sporadic noninherited stage III-IV disease as new patients.

As academic oncologists at large referral centers, we are frequently asked for second-opinion consultations. Initially, we presumed our referral patterns were biased toward seeing a skewed population of young patients. Earlier data had indicated overall survival patterns of young patients were no different from older individuals following standard chemotherapy (5). Subsequently, Lieu et al. (6) determined that the youngest treatment-naïve metastatic CRC patients fared worse with poorer overall survival vs average-age patients when using age as a continuum of care following treatment with modern chemotherapy plus biologic therapy. Despite this intriguing data, young adults with CRC continued to make up only 12% of all CRC patients and were not receiving additional attention (3). However, in 2015, compelling initial data from the Surveillance, Epidemiology, and End Results data base (1975-2010) (7) noted an alarming, unexpected rise in colon cancer (CC; 90%) and rectal cancer (124%) in very young patients (20-34 years) until 2030. The numbers for those aged 35-49 years were less dramatic but still concerning for CC and rectal cancer (28% and 46%, respectively). Siegel et al. (8) confirmed the data were not just limited to the United States but were a global phenomenon. Further analysis revealed that since 1994, the incidence of CRC has been rising by 2% per year in individuals younger than age 55 years (9). Hence, progressive interest over the last decade regarding the etiology, diagnosis, and treatment of early-onset CRC (EO-CRC) has resulted in widespread media attention, support from patient advocacy groups, and additional investigative analyses. Most analyses have failed to demonstrate any unique molecular differences (10), whereas others noted some distinct findings (11).

In 2003, the ACCENT (Adjuvant Colon Cancer End Points) database was created specifically to serve as a pooled resource in early stage CC patients. Originally led by the late visionary statistician Dan Sargent, the ACCENT database has yielded groundbreaking data that has altered how we approach adjuvant therapy (12,13) in CRC, and it continues to inform us. In this issue of the Journal, Jin et al. (14) report their clinical and molecular findings from the ACCENT database and the impact on outcome in early-onset colon cancer (EO-CC; younger than 50 years) vs late-onset colon cancer (LO-CC; 50 years and older) upon review of the ACCENT database. The analysis includes a remarkable sample size of 37 513 stage III patients treated in prospective adjuvant trials. The investigators noted no characteristic differences between the EO-CC and LO-CC regarding patient demographics and pathologic findings. Approximately 25% of patients having mismatch repair (MMR) , *BRAF*, and *KRAS* mutation status had molecular analysis available. This percentage was likely limited because of the time frame of the database, as well as the fact that *RAS* mutation status is not commonly ordered in early stage patients given the lack of utility for anti-epidermal growth factor therapy in the adjuvant setting (15). The investigators concluded that EO-CC relative to LO-CC patients were more likely to present with deficient MMR (dMMR; 16.4% vs 11.5%) and less likely to have *BRAF* V600E. Given the lack of germline mutation data available, and their young age, it is presumed the majority of EO-CC patients had Lynch syndrome. Although these findings are not definitive, it reaffirms the importance of genetic testing and the need for referral to genetic counselors to rule out hereditary CRC syndromes. This could be highly meaningful for the patient and family members for primary and secondary cancer prevention. Multivariate analysis revealed EO-CC patients had improved

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outcomes overall for disease-free survival, overall survival, and survival after recurrence vs their older counterparts. It should be noted that the results of this analysis may be potentially confounded by the heterogeneity of the 25 clinical trials chosen involving chemotherapy, some of which are ineffective in the adjuvant setting (eg, irinotecan, cetuximab, bevacizumab). It should be noted that the ACCENT database was limited to CC patients, and although EO-CC patients represented 17.5% of the patient population, only a minority of these EO-CC patients (n = 1766) were aged 40 years or younger. Therefore, the conclusions from the ACCENT database specific to this analysis only provide limited data relative to the global concerns of identifying the etiology of EO-CC .

An additional comprehensive approach to evaluate the impact of clinical, histopathologic, and genomic characteristics of EO-CRC vs average-onset CRC (AO-CRC; defined as age 50 years and older) reported by Cercek and colleagues (16), also in this issue of the Journal, is based on a single institution experience spanning from 2014 to 2019 . EO-CRC patients were substratified into 2 subsets: ages 35 years and younger and 36-49 years. Formalin-fixed and paraffin-embedded tissue samples with matched controls were available in most patients (1356 of 1446; 94%) allowing for extensive next-generation sequencing using the in-house IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) assay. Germline mutation analysis was provided with patient consent. Despite this large comprehensive analysis, the investigators noted no genomic differences and no differences in overall outcome of EO-CRC vs AO-CRC patients. As a single institution analysis, this resulted in a homogenous patient population in which approximately 50% of patients within each age group were diagnosed with stage IV disease and in which 70% of all treatment-naïve patients received FOLFOX (Folinic acid, Fluorouracil, and Oxaliplatin) plus or minus bevacizumab. In contrast to the ACCENT analysis by Jin et al. (14), the analysis by Cercek et al. (16) was inclusive of all stages and included rectal cancer patients, and patients with known dMMR status and inflammatory bowel disease were excluded. Cercek et al. (16) also noted that clinical presentation of bright red blood per rectum and abdominal pain was more frequent in the EO-CRC patients relative to their AO-CRC counterparts. However, it is difficult to determine the clinical significance of these symptoms given that these EO-CRC patients likely did not recognize early signs and symptoms, had no known family history, and would not have been screened because they were aged younger than 50 years. It is informative that a high number of pathogenic germline variants (23.1%) were noted in the youngest subset (35 years and younger) of patients despite excluding patients at risk for dMMR and other known high-risk factors.

Collectively, what can be elucidated by both studies (14,16) as to the etiology for the unexpected rise in locally advanced EO-CC and metastatic EO-CRC? Neither study can provide the definitive causality for EO-CRC. However, both studies provide statistically significant value to existing literature given their large sample size and similar findings. Although neither study noted differences in clinical staging or genomic landscape, both studies demonstrated the potential impact of an unknown germline mutation: there was an increased likelihood in the ACCENT database data for germline variants for early stage disease (14), whereas Cercek et al. (16) have definitively determined the high percentage of germline variants in those patients aged younger than 35 years. Once again, these studies reaffirm the importance of germline testing in young adults and the necessity of a referral for genetic counseling for evaluation. In turn, pediatricians, family care physicians, and/or primary care providers should carefully review the family history of their young patients with family members.

What are the limitations of both studies? Both analyses are similarly flawed by selection bias. The ACCENT database was derived from patients who participated in largely phase III clinical trials from 2003 to 2019 (14), and the Cercek et al. data stems from a large, top-ranked, academic referral center (16). As a result, all participants (EO-CC, EO-CRC, LO-CC, AO-CRC) are likely to have above-average Eastern Cooperative Oncology Group performance status, are unlikely to be diverse in ethnicity and cultural background, and are likely to be of similar, higher socioeconomic backgrounds. Furthermore, the comparative group for both studies had a median age of 61 years, which is younger than the average-age patient in the general community.

What data has been derived thus far to account for the potential etiology for EO-CRC? As mentioned by both groups of investigators, the etiology for EO-CRC is multifactorial. We are aware of the propensity of obesity in certain geographic regions (17) and its associated risk of CRC, as well as the impact of developing obesity over time resulting in an increased likelihood of EO-CRC (18). Areas of additional exploration and development include evaluating the role of the microbiome on carcinogenesis extending from antibiotic exposure (19,20) as well as the possible link between obesity and dysbiosis in the development of CRC (21,22).

With progressive awareness of EO-CRC largely because of providers, patients, and patient advocates, the American Cancer Society conducted a systematic evidence review with simulation modeling as provided by the Cancer Intervention and Surveillance Modelling Network (CISNET) resulting in a qualified recommendation for the reduction of screening age from 50 years to 45 years for average-risk individuals in 2018 (23). As of May 18, 2021, the US Preventive Services Task Force (USPSTF) also followed suit based on systematic review and modeling as provided by CISNET resulting in a B recommendation noting moderate benefit in reducing mortality and increasing life-years gained (24). We support these changes that definitely bring us one step closer in assisting in the prevention as well as detection of earlier stage disease. However, it is well documented that progression from adenoma to an adenocarcinoma takes 5-10 years (25,26). Hence, for a patient aged 40 years, it is likely the development of a polyp may have originated in his or her early to mid-30s. Therefore, we must continue to educate young adults and their providers (pediatricians, family practice, and/or primary care providers, etc) about early recognition and the potential signs and symptoms of CRC. The USPSTF provides additional diagnostic tests for those who are wary of a colonoscopy (24). The importance of any recommended screening rather than no screening cannot be overemphasized when a patient presents with potential symptoms. A colonoscopy remains the gold standard and can be lifesaving.

In the interim, how can we best support the unmet needs of our existing EO-CRC patient population? We can do so by recognizing that they face unique obstacles compared with their average-age counterparts. It is our duty as medical providers to discuss real-world topics that are often underrecognized and may be difficult to discuss, such as family planning, fertility, sexual dysfunction, psychosocial issues, job security, mental health, overall quality of life, and longevity. Several resources are available to assist medical providers in this discussion for our young patient population. But it is up to us as providers to initiate the discussion.

For many of us who have been assisting in the care of these young adults, we serve as their voices in the medical community. It is our duty to continue to educate physicians, patients, and families about the signs and symptoms of EO-CRC and continue to support research efforts to identify additional causality for EO-CRC.

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