Who is at Risk for Early-onset Colorectal Cancer?

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Modern medical decision-making, whether preventive, diagnostic, or therapeutic, emphasizes the risk-stratification of patients, and is heavily informed and influenced by evidence-based guidelines. Such guidelines for colorectal cancer (CRC) screening were first published in 1997[1], and subsequently by multiple professional organizations. Although there have been disagreements regarding choice of screening modality, the start age of 50 years for most average-risk individuals (with the notable exception of African Americans) has been mostly unchallenged. CRC screening, in those 50 and older, is effective and has been one of the success stories of modern medicine: increased screening uptake, early detection, and improved therapeutic options have contributed to a steady decline in CRC incidence and mortality rates in the U.S.[2] However, this progress has been tempered by the rise in CRC incidence among those less than 50 years of age (so-called early-onset CRC).[3] In fact, 10-12% of all CRCs are diagnosed in patients younger than the age of 50, and these cancers tend to be more advanced-and devastating-at presentation.[4,5,6] Even more alarming is the rise in the CRC-associated mortality rate among this young cohort.[7] These trends call for greater understanding of risk factors associated with early-onset CRC, with the rationale that incorporating these risk factors into existing preventive strategies will extend the benefits of screening to individuals younger than 50.

Intuitively, it would seem that hereditary factors could be a major contributor to the burden of early-onset CRC. In reality, however, the evidence does not support this. Stoffel et al. reviewed data from the University of Michigan Comprehensive Cancer Center comprising patients who were diagnosed with CRC at age <50 and had undergone genetic risk assessment between 1998 and 2015. Among patients with early-onset CRC, 1 in 5 carried a germline genetic

mutation, about one quarter had a first-degree relative with CRC, and the majority of individuals did not have any family history of CRC or hereditary CRC syndromes.[4,8] These findings do not imply that hereditary causes of early-onset CRC are not important, but they do underscore that we are dealing with a complex phenomenon, likely driven by both biologic and environmental factors.

An important observation is that early-onset CRC seems to be a disease of affluence: the rising incidence, without a concurrent rise in older adults, is particularly notable in high-income countries, including the U.S., Australia, Canada, Germany, Denmark, New Zealand, and the United Kingdom.[9,10] This has raised the question of whether changes in dietary patterns, and the accompanying increase in obesity rates, are potential contributors. The parallel trend between cancer and the obesity-epidemic extends beyond CRC. Sung et al. reported that several obesity-related cancers have increased in incidence from 1995 to 2014, including cancers of the uterus, gallbladder, kidney, and pancreas, and multiple myeloma. However, the rise in incidence limited to younger adults is a phenomenon unique to CRC. Several other factors have been associated with early-onset colorectal neoplasms and CRC, including early-life antibiotic exposure,[11] smoking (although the prevalence of smoking has been decreasing), alcohol use, and processed meat consumption, though these findings are not consistent.[12]

In this issue, Gausman et al. report results from a large retrospective study that aimed to identify sociodemographic and clinical factors associated with early-onset CRC.[13] The authors used ICD-9 and ICD-10 codes to identify patients 18 years of age and older who were diagnosed with CRC between 2011 and 2017 at a single academic center. They compared 269 patients who were 18-49 years of age (defined as early-onset) to two groups: 1) 2802 who were 50 years

and older (late-onset) at time of diagnosis of CRC, and 2) 1122 age-matched controls without a history of CRC. Most early-onset CRC patients (73%) were 40-49 years old at the time of diagnosis, 54% were 45 and younger, and 13% had a family history of CRC; of these, half had a first-degree relative with CRC and should have undergone screening before the age of 50. The remaining 252 (94%) patients were considered at average-risk for CRC based on current guidelines. Consistent with prior studies, Gausman et al. found that early-onset CRC patients were more likely to present with cancers in the left colon or rectum, and with more advanced stage.

Compared to the CRC-free controls, early-onset patients were more likely to be male, have a personal history of inflammatory bowel disease (IBD), and a family history of CRC. Interestingly, there were no significant differences in race, body mass index (BMI), tobacco use, and comorbidities including coronary artery disease, hypertension, stroke, and diabetes. When compared to the late-onset CRC cohort, early-onset CRC patients were also more likely to be male, have a personal history of IBD, and a family history of CRC. However, black or Asian race were found to be associated with early-onset CRC, which was not seen with the comparison to CRC-free controls. Comorbidities such as obesity and diabetes were not compared between the early- and late-onset CRC patients given that these factors, as noted by the authors, are confounded by age. The authors also performed a sensitivity analysis, excluding patients with IBD and family history of CRC, with no impact on the results. The overall conclusion was that non-modifiable risk factors, rather than modifiable ones, were associated with early-onset CRC.

In contrast, several studies have shown modifiable risk factors such as obesity, physical activity, dietary habits, tobacco use, and diabetes to be associated with early-onset CRC. Liu et

al. studied a cohort of women 25-42 years of age enrolled in the Nurses' Health Study II (NHS II) and found that obese women (BMI ≥30) had nearly a two times greater relative risk of early-onset CRC as compared to women with BMI 18-22.9 (RR=1.93; 95% CI 1.15-3.25).[14] Nguyen et al. also evaluated sedentary behaviors in the same cohort and found that sedentary behavior (defined by TV viewing time) was associated with early-onset CRC independent of obesity and exercise.[15] Similarly Kim et al. studied patients <40 years of age in South Korea and found that regular exercise was one of the few protective factors for colorectal neoplasia among those 30-39 years of age.[16] Rosato et al. analyzed data from three case-control studies on CRC performed in Italian and Swedish cohorts between 1985 and 2009.[12] In comparison to CRC-free controls, they found several dietary associations with early-onset CRC patients including: heavier alcohol use (≥14 drinks per week), increased processed meat intake, and lower consumption of vegetables, fruits, and fish. Finally, smoking and diabetes have also previously been shown to be associated with colorectal neoplasia, even among those <50 years of age.[17,18] Although Gausman et al. did not find a difference in tobacco use or diabetes when comparing early-onset CRC to CRC-free controls, they did not include these factors in their comparison between the early-onset and late-onset CRC cohorts. While it is possible that duration of exposure to these factors could have confounded results, their modifiable nature makes them targets worthy of additional study in early-onset CRC patients.

So why is modifiable versus non-modifiable an important issue? We live in the era of risk-stratification and personalized screening, yet the ability to apply these approaches to early-onset CRC is currently limited. An inevitable, and somewhat nihilistic, argument is to cast away tailored approaches and offer screening to everyone. Could population-based screening with

integration of non-modifiable risk factors including age and family history, similar to patients 50 and older, be the answer? The American Cancer Society (ACS) espoused this view, with the recently published, and widely debated, qualified recommendation to initiate CRC screening at the age of 45 in all average-risk individuals.[19] However, in the study by Gausman et al., more than half of patients with early-onset CRC were diagnosed at an age younger than 45. CRC in these patients would not have been prevented by application of the ACS guidelines.

The study by Gausman et al. highlights several non-modifiable risk factors that are associated with early-onset CRC, but many unanswered questions remain, including the over-arching controversy of whether to extend universal or selective screening to 45 to 49 year-olds. Currently, there is simply a dearth of empirical evidence to guide the development and implementation of effective and widely-accepted screening approaches for these patients.[20] Despite these uncertainties, the CRC incidence and mortality trends among those <50 years of age should not be considered irreversible. We should continue efforts to understand the factors driving early-onset CRC, and how best to prevent this scourge.

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