Early-Onset Colorectal Cancer: A Call for Greater Rigor in Epidemiologic Studies

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ABSTRACT

The rates of early-onset colorectal cancer (EO-CRC) have been rising by 0.5% to 2.4% annually for three decades, accounting for an estimated 12% of all colorectal cancer diagnosed in the United States in 2020. Enhancing the rigor and comprehensiveness of the epidemiology in terms of the exposures and prognostic biomarkers is essential if we are to modify risk factors and underlying mechanisms, ultimately arresting this unduly trend. This commentary serves to describe the disease trend, postulate underlying risk factors and mechanisms driving disease incidence, and proposes a call to action for cancer epidemiologists to promote increased and timely opportunities to intervene on this trend.

Introduction

From the mid-1990s to current times, the rate of early-onset colorectal cancer (EO-CRC), or disease diagnosed among adults under 50 years of age, has increased for both colon and rectal cancers annually, a trend alarmingly opposite to that of disease incidence after the age 50 years (**Fig. 1**). Current estimates suggest we will experience up to 124% increase in EO-CRC by 2030 should nothing change (1), with the most rapid increase predicted among individuals in the range of 20 to 34 years of age (1). Interpretation of these data suggests a birth-cohort effect (2) that interestingly is observed across the globe (3) and could continue should causal factors not be identified. It is possible that this birth-cohort effect of increased colorectal cancer risk may extend even beyond younger ages. Of concern, the more recent flattening (versus previous downward trends) of rates observed among older age groups (50–69 years) could very well represent the early stages of such a phenomenon, in which the increased risk could have a multiplier effect in combination with well established age-related increases in colorectal cancer incidence. It is therefore imperative to consider the possibility that EO-CRC may only be the beginning of an increase in colorectal cancer at all ages, that will become evident as the current young population ages and reaches later stages of life. Additionally, should epigenetic changes be drivers of risk, there is a significant possibility that future generations will demonstrate similar trends.

From the mid 1990s to 2010, the rising incidence of EO-CRC was largely driven by rectal disease (2). Since 2012, however, similar increasing rates of colon and rectal cancers less than 50 are noted (4). EO-CRC is characterized by late stage at diagnosis (5), microsatellite instability and mucinous, signet ring and/or poorly differentiated tumors (6), and driven by rates in non-Hispanic whites (4).

Some risk factors for EO-CRC are shared with later-onset disease, including family history and inflammatory bowel disease (7, 8). Modifiable risk factors that are associated with colorectal cancer risk include obesity, diet (red and processed meat, alcohol), tobacco use, physical inactivity, and protective factors such as aspirin and/or calcium supplement use (9, 10). The aforementioned risk factors generally demonstrate an association with colorectal cancer independent of age, however the birth-cohort effect suggests that early life exposures specifically, are critical for understanding the etiology of EO-CRC (11). Age-period cohort (APC) models have investigated age effects (reflecting biological changes) and period and cohort effects (reflecting environmental changes) in relation to increasing patterns of obesity and diabetes in younger populations (12). The development of a conceptual framework (potentially based on the already established obesity and diabetes frameworks, and inclusive of genomics, proteomics, and metabolomics) for how an observed cohort effect related to EO-CRC is warranted.

Future efforts in epidemiology must address the shortfalls in our current data collection and analyses related to EO-CRC if we are to inform hypothesis-driven interventions. While pooling efforts are underway to increase the statistical power to evaluate associations between exposures and risk, these efforts must be combined with more intentional exposure measurement. Specifically, data on early life modifiable exposures must be collected in relation to prenatal exposures to alcohol, tobacco, recreational drugs, and even pharmaceuticals, or even folic acid or other nutrients. Early life stressors such as poverty and food insecurity or abuse may also inform on risk as may life-course variables such as weight trajectory across the lifespan, physical inactivity, and sedentary behavior. Additionally, there may be reason to evaluate the role of bacteria and other colonizing/infectious agents (such as the recently reported Orthobunyavirus) in disease risk given the increase in rectal cancer and the role of human papillomavirus (HPV) in cancer promotion (13). Beyond understanding earlier life exposures, it is imperative to collect more robust data in relation to other variables. For example, body mass index (BMI) does not provide the rigor of adiposity exposures that can be gained through

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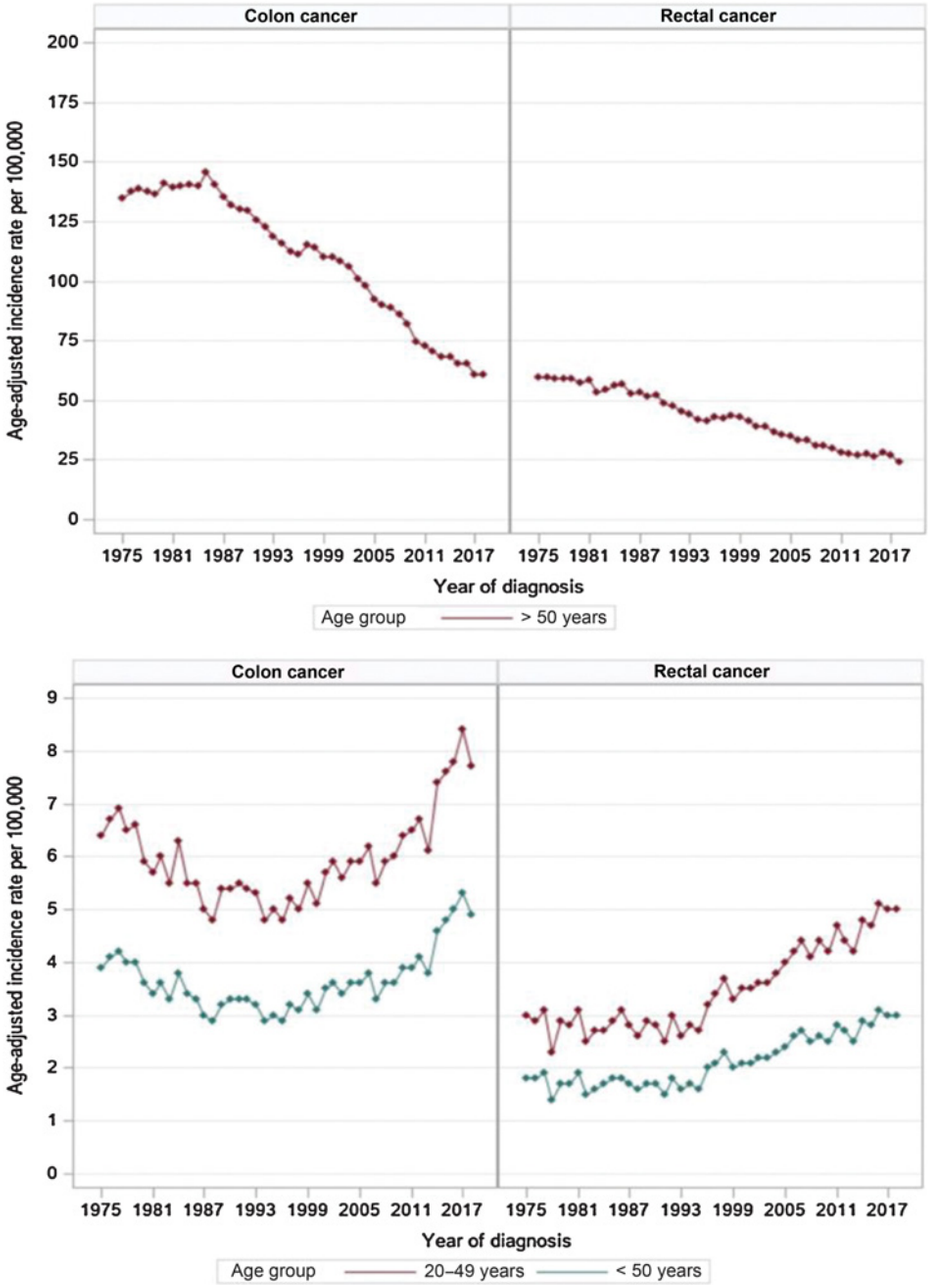

Figure 1.
Age-adjusted incidence rates of colon and rectal cancer cases (1975–2018). This figure presents the increasing trend of colorectal cancer incidence among individuals aged 0 to 49, <50, and >50. The graph was created using Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Research Data, 9 Registries, Nov 2020 Sub (1975–2018) – Linked To Country Attributes – Time Dependent (1990–2018) Income/Rurality, 1969–2019 Counties, NCI, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.

body composition and specifically abdominal visceral fat analysis (14). Self-reported diet does not accurately capture exposure to diet (including common protective factors such calcium and fiber), nor does it rigorously assess diet-related cancer promoters such as Advanced Glycosylated End-products (AGES), that are increasingly associated with colorectal cancer and should be interrogated in the setting of EO-CRC disease risk. More robust data collection methods are needed, since BMI or self-reported diet do not accurately capture exposure related to body weight or diet. We would like to highlight the substantial potential of automated body composition assessment using CT scans and the validation of dietary intake by correlating self-reported dietary intake with circulating biomarkers (metabolomics). These methods may help us elucidate the etiology of early-onset colorectal malignancies through meaningful and robust discovery of the role of diet and body weight.

Known and Postulated Risk Factors

Risk factors for EO-CRC identified to date suggest there may be unique predisposing risk factors which include prenatal exposures such as *in utero* tobacco and antibiotics that lead to low birthweight infants and potentially upregulation of genes associated with energy utilization and/or methylation (15, 16); metabolic dysregulation independent of elevated BMI (17); changes in the gut microbiome associated with C-section delivery and/or early life antibiotic use (5); sedentary behavior (18); Western dietary pattern (which includes

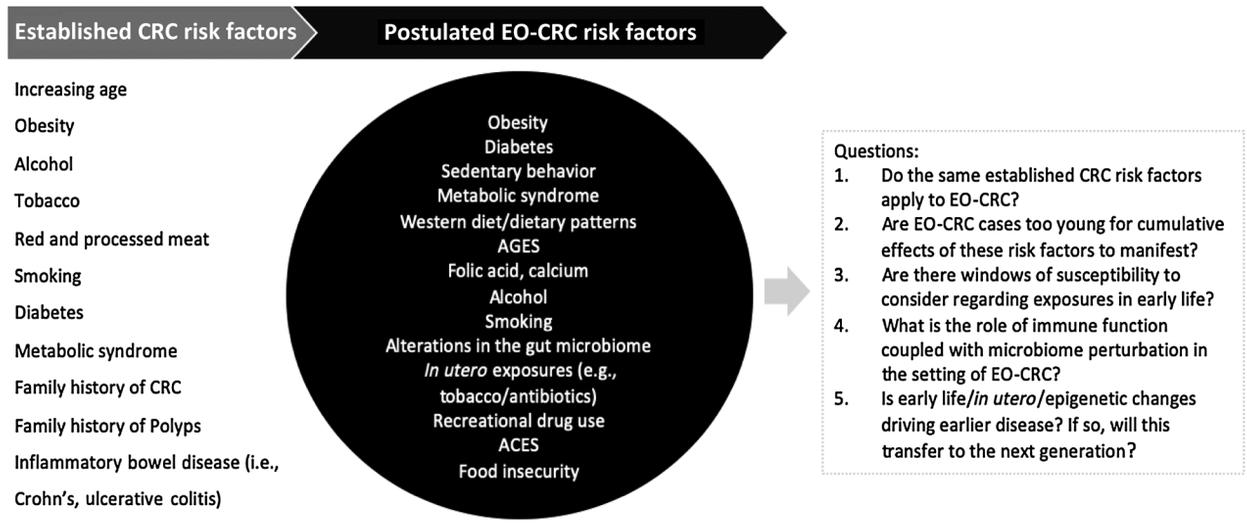

Figure 2.
Epidemiologic data on EO-CRC. This figure presents known/established risk factors for colorectal cancer as well as postulated risk factors described in this commentary. In addition, this set of established and postulated risk factors raises important questions to be considered, which are also presented in this figure. CRC, colorectal cancer.

refined carbohydrates, red/processed meat, and fructose consumption in the form of sugar sweetened beverages; ref. 19); as well as various *in utero* and early life social exposures and adverse childhood experiences (ACES) that drive our stress response, including inflammation and oxidative stress (20), known hallmarks of cancer (**Fig. 2**). Importantly, recent work has observed that greater parity in females is associated with reduced risk of EO-CRC (21). Engaging in future work to not only understand potential inciting (risk) factors but also potential protective factors in this younger population is warranted.

We postulate that there could potentially be underlying (perhaps undiagnosed) metabolic dysregulation with or without immune suppression, infection, or abnormal colonization/dysregulation of existing viruses and/or bacteria, or other potential inciting factors. Whether specific phenotypes associate with EO-CRC has not been well studied. Importantly, phenotype and risk factors may be expressed differentially by sex, as has been suggested for obesity in EO-CRC in women (22), and diabetes, hypertension, hyperlipidemia, and smoking in men (23). Race and ethnicity may also be associated with risk, with differential and greater risk among Asian and Black populations (7), suggesting that social determinants of health, may contribute to risk. Furthermore, rectal cancer (versus proximal or distal colon cancer) may represent a very different risk profile when it comes to metabolic dysregulation and colorectal cancer (24), although insufficient sample size has precluded robust evaluation by anatomic sites in the majority of epidemiologic studies.

Role of Epigenetics

Another aspect of EO-CRC that has garnered attention is related to epigenetic changes. Epigenetic alterations are those that alter an individual's phenotype in the setting of an unchanged underlying genotype. These variations include methylation and histone modification, both of which have been shown to be associated with an overall risk of colorectal cancer (25). Although to date there are a dearth of studies of epigenetic changes such as methylation or histone modification among EO-CRC cases, prior studies provide a glimpse of potential drivers. Results from studies comparing differential rates of methylation of key genes in the carcinogenesis pathway (when compared with unaffected individuals) remain equivocal, and further work is required to fully understand whether epigenetic modifications observed in patients with EO-CRC are similar to those of older individuals with colorectal cancer, as well as which changes may have the greatest significance on pathology. Findings regarding epigenetic changes will allow for a better understating of which exposures may elevate risk, as well as providing important information regarding potential drug targets and preventative agents.

Systemic Biomarkers

Finally, recent advances into systemic biomarkers indicate that certain clinical and molecular features may differentiate patients with EO-CRC from older patients. These findings have implications for not only identifying and diagnosing EO-CRC in its earliest stages, but may also influence treatment options (e.g., targeted therapy for patients with MSS *BRCA2* mutations, immunotherapy/checkpoint inhibitors for patients with POLE or POLD hyper mutated tumors; ref. 6). This continues to be an area of active clinical and scientific investigation.

Existing Studies

There are elements of existing studies that may inform on the etiology of early-onset colorectal cancer such as potential lifestyle factors and other clinical data (e.g., aspirin use, antibiotic use). However, there are methodologic considerations with existing studies that should be noted. The greatest limiting factor regarding the use of existing studies is the limited sample size, driven by the relatively rare nature of this disease (albeit increasing at an alarming rate) and availability of biospecimen data (blood, urine, tumor tissue) among young colorectal cancer cases under the age of 50. Importantly, the most rapid increase in EO-CRC is predicted among individuals aged 20 to 34. Existing data available regarding this specific population is even more limited. Pooling existing prospective cohort studies to

obtain sufficient sample sizes may be the most effective approach to investigating EO-CRC, however there are inherent limitations with this approach: (i) there is limited time (duration of exposure) from baseline data collection to diagnosis, since many cohort studies begin enrollment at later ages; (ii) while some cohort studies have collected data on body weight or diet intake earlier in life (e.g., high school), very few cohort studies have collected data on early life exposures which is particularly critical given the birth-cohort effect associated with EO-CRC; (iii) given that EO-CRC is largely driven largely by a birth-cohort effect (with those born after 1950s as the cohort at greatest risk), cohort studies are generally all assembled at different calendar times. Thus, adjustments for associations with the diet, clinical, or other lifestyle factors would need to be made among cohorts dominated participants born prior to the 1950s; and (iv) because the major increase in EO-CRC is largely driven by rectal cancer, a focused analysis regarding lifestyle exposures on risk of early-onset rectal cancer specifically, is warranted. Any subanalysis on tumor location, sex, or other variables of interest would most likely be underpowered and only provide "exploratory" findings.

Summary

In summary, several improvements in approaches to EO-CRC are necessary to support meaningful and timely advancements in understanding this disease. We therefore propose the following call to action to address a productive epidemiologic path forward in order to mitigate the rising trend of EO-CRC among our young population.

- Recognize EO-CRC as a unique disease, perhaps on a continuum from early to intermediate to later age disease, likely with its own risk profile;
- Develop a framework for investigating birth-cohort effects, such as increasing EO-CRC;
- Exposure data must be expanded to include longitudinal collection of early life exposures from prenatal through adulthood, along with biospecimen collection;
- Investigation into the physiologic effects transferred to the developing fetus (umbilical circulation, amniotic fluid) and from mother to newborn through breastfeeding;
- Exposure characterization should be expanded to include antibiotic use, aspirin use, early life events/stressors, ingested chemicals related to food preservation and food colorants;
- Exposure estimates must be more precise and rigorous including assessment of body composition, microbiome, metabolome;
- More rigor in lifestyle behavior exposure estimates through the application of nutritional biomarkers, accelerometry, cotinine levels, etc.;
- Expanded dietary factors such as AGEs and other food processing and preparation factors;
- Temporality of exposures may be important to disease risk and progression;
- Early and repeat measures of metabolic health should be integrated into analyses;
- Pooling of cases to support statistical power to evaluate risk profiles by race, ethnic, sex, and other subgroups through existing cohorts.
- Consider the possibility that EO-CRC may only be the beginning of an increase in colorectal cancer at all ages, that will become evident as the current young population ages and reaches later stages of life. Additionally, should epigenetic changes be drivers of risk, there is a significant possibility that future generations will demonstrate similar trends.

Authors' Disclosures

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