Elucidating the Drivers for the Rising Incidence of Early-Onset Colorectal Cancer: How Ecologic Studies Could Help and What Is Next

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ABSTRACT

The incidence of colorectal cancer diagnosed before age 50, often referred to as early-onset colorectal cancer, has been increasing, whereas the overall colorectal cancer incidence has declined. Elucidating the drivers for the rising burden of early-onset colorectal cancer is a priority in cancer epidemiology and prevention. In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Chen and colleagues demonstrated that ecologic studies are a helpful method to reveal emerging risk factors at the population level and concluded that alcohol use might be a potential contributor to the rising incidence of early-onset colorectal cancer. Moving forward, because of the observed birth cohort effect in early-onset colorectal cancer, where younger generations have a steeper increase, hypothesis-driven investigations on emerging risk factors in recent generations, especially during early life, are warranted. Ultimately, the identified risk factors could be integrated with well-established microsimulation models of colorectal cancer, powerful tools that can simultaneously capture population-level secular changes in risk factors, relative risk estimates for each risk factor, and the natural history of colorectal cancer. This would allow us to quantitatively estimate the explained and unexplained portion of the rising incidence of early-onset colorectal cancer by calendar period and birth cohorts, and to help identify priorities in etiologic research, prevention, and early detection.

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Colorectal cancer is the second most common cause of cancer deaths in the United States (1). While the overall colorectal cancer incidence has declined, incidence rates of early-onset colorectal cancer, commonly defined as colorectal cancer diagnosed before age 50, have increased since the mid-1990s and recently by 2.2% annually from 2012–2016 (2). It is crucial to better understand the potential drivers of the rising incidence of early-onset colorectal cancer to guide prevention efforts.

In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Chen and colleagues examined the ecologic association between dietary factors and early-onset colorectal cancer in the US. Unlike cohort studies that use data from individuals, their ecologic study used population-level data by linking datasets from the National Health and Nutrition Examination Surveys (NHANES), the National Health Interview Surveys, and the Behavioral Risk Factor Surveillance System (3). They stratified the population by 5-year age groups (25–49), 5-year periods (1977–2016), race (white and black), and sex (men and women; ref. 3). Negative binomial regression models were applied to study the association between dietary factors and early-onset colorectal cancer incidence. Notably, the authors introduced two unique approaches to address the issues of time lag from exposure to disease and potential confounding by age. To take into account the latent period between exposure and disease onset, they leveraged exposure 10 years ahead of the outcome (lagging the outcome) or cumulative exposure over the 10 years before the outcome. The lag time of 10 years was chosen on the basis of data availability and the assumed induction time from exposure to disease initiation (3), although the true induction time could vary by the type of exposure, age at the time of exposure, and exposure duration. To minimize confounding by age, they introduced an age-mean centering approach, where the age-specific mean exposure for each age was subtracted to remove the age association with exposure (3). Compared with traditional ecologic analyses, their advanced statistical approaches improved the ability to reveal meaningful associations for potential risk factors.

Their study also highlighted the utility of ecologic studies to investigate risk factors for early-onset colorectal cancer. Due to the low absolute risk of early-onset colorectal cancer, a very large sample size would be needed to allow sufficient statistical power in traditional cohort or case–control studies. Ecologic studies, on the other hand, can take advantage of large-scale population data to examine a wide range of potential risk factors. In addition, using available national datasets such as NHANES, ecologic studies could be conducted in a relatively quick and inexpensive way. However, ecologic studies also have their limitations. Most notably, correlations identified at the population level may not hold true for individuals, often referred to as ecologic fallacy (4).

Through ecologic analysis, Chen and colleagues concluded that at the population level, alcohol consumption had a positive association with early-onset colorectal cancer. They further proposed that alcohol use might have contributed to the rise in colorectal cancer incidence in young adults in the US, considering the lagged, concordant trends of alcohol consumption and early-onset colorectal cancer (3). Their findings were generally consistent with results from recent

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international consortium analyses using data pooled from 13 population-based studies, which showed that heavier alcohol use (>28 g/day) was associated with an increased risk of early-onset colorectal cancer [OR = 1.25; 95% confidence interval (CI), 1.04–1.50] compared with 1 to 28 g/day (5). Similarly, a number of other international studies also suggested a connection between alcohol use and early-onset colorectal cancer, with a dose-dependent association (6–8). While these studies were mostly case–control studies and more prospective studies are needed, a recent prospective analyses in three US cohorts reported that alcohol consumption ≥ 15 g/day in early adulthood (age 18–22) was likely associated with a higher overall colorectal cancer risk (HR = 1.28; 95% CI, 0.99–1.66; $P_{trend} = 0.02$; $P_{heterogeneity} = 0.44$), regardless of age of diagnosis (9). More studies are needed to elucidate the association between alcohol use throughout the life course and the risk of early-onset colorectal cancer.

The authors acknowledged a few limitations in their work, including not considering the birth cohort effect. Birth cohort effect is defined as variations in the risk of a health outcome according to the birth year (10). In the context of rising early-onset colorectal cancer incidence, certain risk factors that have emerged with time might have differentially affected the younger age groups and changed their risks for colorectal cancer. It is thus worthwhile to consider emerging risk factors with parallel increases in recent birth cohorts, especially those in early life that could have continued to exert influence later in life, manifested as a delayed upward trend in early-onset colorectal cancer incidence. Indeed, many studies have pointed out that exposures to risk factors in early life could be critical to colorectal cancer development (11–13). Recent data revealed positive associations between adolescent and early adulthood obesity and the risk of early-onset colorectal cancer (14, 15). Notably, the adolescent obesity prevalence in the US has increased significantly from 6.1% in 1971–1974 (16) to 21% in 2018 (17). Investigating obesity during a period of growth and development in childhood and adolescence could potentially offer new insights into the risk factors of early-onset colorectal cancer. Besides obesity, diet in childhood and adolescence may likely play a key role in colorectal cancer carcinogenesis at younger ages (18, 19). While validation is needed, a recent prospective analysis in the Nurses' Health Study II suggested that sugar-sweetened beverage consumption in age 13 to 18 years was associated with the risk of early-onset colorectal cancer, likely independent of adolescent body mass index and other major confounding factors (20). Such findings were supported by strong experimental evidence that excess fructose in sugar-sweetened beverages induces dysbiosis and impairs gut barrier to lead to colorectal cancer, potentially independent of obesity (21–23). Taken together, hypothesis-driven investigations on emerging risk factors in recent generations, especially during early life, are warranted.

Moreover, the extent to which relevant risk factors contribute individually and collectively to the rise of early-onset colorectal cancer remains to be quantified. To this end, well-established microsimulation models led by the National Cancer Institute (NCI) Cancer Intervention and Surveillance Modeling Network Colorectal Cancer group (CISNET-colorectal cancer; ref. 24) are unparalleled tools to address these unmet needs. Specifically, these models allow for synthesis of strengths of associations from epidemiologic findings, patterns of risk factors representative of those in the US population, disease progression based on adenoma to carcinoma transition, as well as quantification of benefits and burden associated with different screening modalities to assist cancer control planning and policy decisions (25). They are also superior over other traditional methods, such as populational attributable risk (26), in estimating contributions of one or multiple risk factors, because these models additionally capture secular changes of risk factors and the natural history of colorectal cancer progression (27). As such, microsimulation models could play a significant role in research on early-onset colorectal cancer, by providing a better picture of the explained and unexplained portion of the rising incidence by calendar period and birth cohorts, to facilitate the identification of future research priorities, and to assist targeted screening and early detection efforts.

In summary, the increasing incidence of early-onset colorectal cancer challenges us to reevaluate our existing knowledge about colorectal cancer and to identify emerging risk factors, by leveraging diverse, rigorous analytical approaches and data sources. Well-performed ecologic studies, using novel approaches to reveal associations at the population level while mitigating ecologic fallacy, can be used for initial hypothesis generation to guide future studies of other types. As we continue to elucidate risk factors for early-onset colorectal cancer, more attention should be paid to early life exposures, given the observed birth cohort effect. In addition, microsimulation models are powerful tools to elucidate the drivers for the rising incidence of early-onset colorectal cancer.

Authors' Disclosures

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