NARRATIVE REVIEWS

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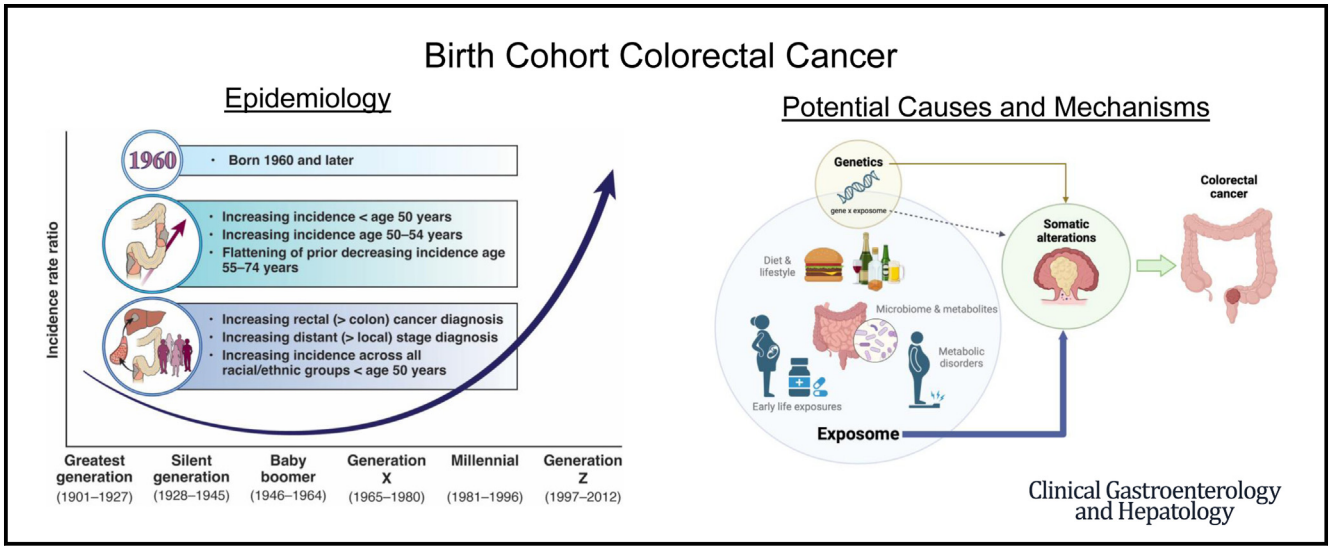
Birth Cohort Colorectal Cancer (CRC): Implications for Research and Practice

Samir Gupta,[1,2] Folasade P. May,[3,4,5] Sonia S. Kupfer,[6] and Caitlin C. Murphy[7]

[1]Section of Gastroenterology, Jennifer Moreno San Diego VA Medical Center, San Diego, California; [2]Division of Gastroenterology, Department of Medicine, and Moores Cancer Center, University of California, La Jolla, California; [3]Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California; [4]Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California; [5]UCLA Kaiser Permanente Center for Health Equity, Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California; [6]Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Chicago, Chicago, Illinois; and [7]Department of Health Promotion & Behavioral Sciences, University of Texas Health Science Center at Houston (UTHealth Houston) School of Public Health, Houston, Texas



Colorectal cancer (CRC) epidemiology is changing due to a birth cohort effect, first recognized by increasing incidence of early onset CRC (EOCRC, age <50 years). In this paper, we define "birth cohort CRC" as the observed phenomenon, among individuals born 1960 and later, of increasing CRC risk across successive birth cohorts, rising EOCRC incidence, increasing incidence among individuals aged 50 to 54 years, and flattening of prior decreasing incidence among individuals aged 55 to 74 years. We demonstrate birth cohort CRC is associated with unique features, including increasing rectal cancer (greater than colon) and distant (greater than local) stage CRC diagnosis, and increasing EOCRC across all racial/ethnic groups. We review potential risk factors, etiologies, and mechanisms for birth cohort CRC, using EOCRC as a starting point and describing importance of viewing these through the lens of birth cohort. We also outline implications of birth cohort CRC for epidemiologic and translational research, as well as current clinical practice. We postulate that recognition of birth cohort CRC as an entity—including and extending beyond rising EOCRC—can advance understanding of risk factors, etiologies, and mechanisms, and address the public health consequences of changing CRC epidemiology.

Keywords: AAPI (Asian-American/Pacific Islander); Birth Cohort; Black/African-American; Colorectal Cancer; Diverse/Diversity; Early Onset Colorectal Cancer; Epidemiology; Equity; Hispanic/Latinx; Native American/Indigenous/American Indian; Race/Racial; Racial/Ethnic Disparities; Socioeconomic; White/Caucasian.

Birth Cohort Colorectal Cancer: A New Phenomenon

Colorectal cancer (CRC) epidemiology is changing due to a birth cohort effect, first recognized by increasing incidence of early onset CRC (EOCRC, age <50 years) among

Abbreviations used in this paper: **AI/AN, American Indian/Alaska Native; APC, annual percent change; API, Asian or Pacific Islander; BMI, body mass index; CI, confidence interval; CMS, consensus molecular subtypes; CRC, colorectal cancer; EOCRC, early onset colorectal cancer; MSI, microsatellite instability; OR, odds ratio; PFAS, perfluoroalkyl and polyfluoroalkyl substances; RR, relative risk; U.S., United States.**

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individuals born 1960 and later (also previously described as among individuals born 1950 and later).[1] Cohort effects are broadly defined as changes across a group or population who experience the same initial event, such as birth, within a single year or period of years. A birth cohort effect occurs when an outcome, such as incident CRC, is strongly determined by year of birth or birth cohort.[2] Examples of birth cohorts include *Baby Boomers*, born 1946 to 1964, and *Generation X*, born 1965 to 1980. Birth cohorts age through life together and share exposures, which can include historical events, social experiences, and socioeconomic, behavioral, and environmental risk factors for health and disease. From an epidemiologic perspective, a birth cohort effect can be differentially experienced by age groups and can be influenced by time period-related exposures. Myriad birth cohort effects have been described, impacting risk for cancer and other health conditions.[2,3] For example, liver cancer mortality has been shown to be highest among *Baby Boomers*, often attributed to the higher rates of hepatitis C virus exposure in the 1970s and 1980s and the subsequent infections this birth cohort experienced.[4,5]

In this Review, we define "birth cohort CRC" as the observed phenomenon, among individuals born 1960 and later, of increasing CRC risk across successive generations, rising EOCRC incidence, growing incidence among individuals aged 50 to 54 years, and flattening of prior decreasing incidence among individuals aged 55 to 74 years, based on data from the United States (U.S.) (Figure 1). We demonstrate that birth cohort CRC is associated with unique features, including increasing rectal cancer incidence and distant stage CRC diagnosis, and increasing EOCRC across all racial/ethnic groups. We review potential risk factors, etiologies, and mechanisms for birth cohort CRC. Implications of birth cohort CRC for epidemiologic and translational research are outlined. In particular, we recommend future research consider not only age at diagnosis, but also birth cohort to group CRC outcomes and examine etiologies, risk factors, and mechanisms that may explain the changing epidemiology of CRC, such as by restricting analyses to individuals born 1960 and later or comparing influence of a risk factor among individuals born before or after 1960. Further, we identify implications of birth cohort CRC for clinical practice, including importance of redoubling efforts to ensure all individuals currently age-eligible have access to high-quality screening and follow-up, supported by evidence-based practices for increasing screening participation. We postulate recognizing birth cohort CRC as an entity that includes and extends beyond rising EOCRC incidence can advance our ability to understand risk factors, etiologies, and mechanisms, and address the public health consequences of changing CRC epidemiology.

Changing Epidemiology of CRC

Overarching Trends

CRC rates have increased in the U.S. among individuals born since the early 1960s (Figure 1). *Generation X* (approximate birth years 1965–1980) experienced an initial increase in EOCRC,[1,6] and rates subsequently increased among this generation after age 50 years.[7–9] Compared with individuals born in 1950 to 1954, rates are 1.22-fold (95% confidence interval [CI], 1.15–1.29) higher among individuals born in 1965 to 1969 and 1.58-fold (95% CI, 1.43–1.75) higher among individuals born in 1975 to 1979. Rates are now increasing across successive generations, particularly among *Millennials* (approximate birth years 1981–1996) entering mid-adulthood. Specifically, incidence rates are 1.89-fold (95% CI, 1.65–2.51) and 2.98-fold (95% CI,

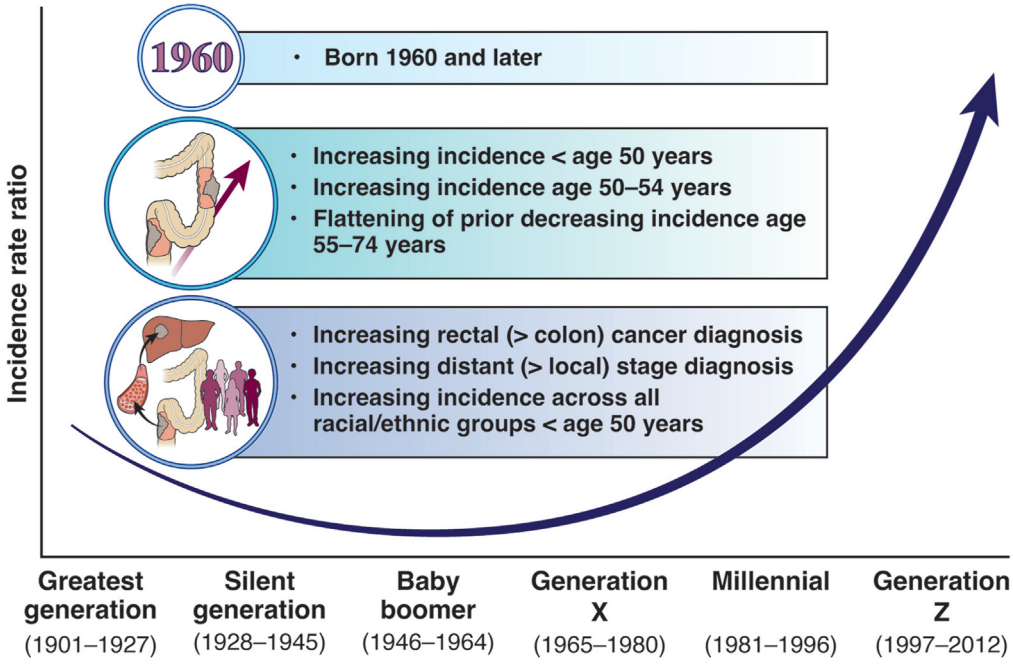

Figure 1. Birth cohort CRC. Birth cohort CRC is defined as the observed phenomenon, among individuals born in 1960 and later, of increasing CRC risk across successive birth cohorts, rising early onset CRC incidence, increasing incidence among individuals aged 50 to 54 years, and flattening of prior decreasing incidence among individuals aged 55 to 74 years. Birth cohort CRC is associated with unique features, including increasing rectal (> than colon) cancer and distant (> local) stage CRC diagnosis, and increasing early onset CRC across all racial/ethnic groups.

2.29–3.87) higher among individuals born in 1980 to 1984 and 1990 to 1994, respectively, compared with individuals born in 1950 to 1954.[10,11] These birth cohort effects are evident on a global scale,[12] despite differences in population age structure, screening programs, and diagnostic strategies across world regions.

Because birth cohorts age and move through life together, it is anticipated that rates of CRC will continue to increase as time goes on and higher-risk birth cohorts become older. Four important shifts in CRC incidence are already apparent: (1) rates are increasing or plateauing through age 60 to 69 years; (2) rectal cancers now predominate through age 50 to 59 years; (3) rates of distant stage disease have more rapidly increased or more slowly decreased compared with local stage disease; and (4) rates of EOCRC are increasing across all racial/ethnic groups. These shifts have resulted in changes in the distribution of age and race/ethnicity among individuals diagnosed with CRC over time, with a higher proportion of individuals younger than age 60 years and non-Hispanic Black, non-Hispanic Asian or Pacific Islander (API), non-Hispanic American Indian/Alaska Native (AI/AN), and Hispanic individuals in 2019 vs 1992 (Figure 2). Figure 3 illustrates shifts for the 50 to 59 year age group. Supplementary Tables 1 to 4 provide annual percent change (APC) in incidence rates for all ages, age <50 years, age ≥50 years, and 5 10-year age groups (age 30–39, 40–49, 50–59, 60–69, and 70–79 years), with additional detail summarized below.

Incidence Rates Increase or Plateau Through Age 60 to 69 Years

As shown in Supplementary Table 1, incidence rates have steadily increased since 1992 for ages 30 to 39 (APC, 2.6; 95% CI, 2.3–3.0) and 40 to 49 (APC, 1.7; 95% CI, 1.5–1.9) years, consistent with well-described increases in EOCRC.[1] There were large decreases in incidence rates for age 60 to 69 and 70 to 79 years, but starting in about 2012, rates decreased more slowly. For example, rates decreased by about 5% per year from 2008 to 2011 for age 60 to 69 years but have since decreased by less than 2% per year. Similarly, for age 70 to 79 years, rates decreased by almost 6% per year from 2008 to 2013, but by 3.6% per year from 2013 to 2019. Confluence of increasing rates for individuals younger than age 50 years and slowing declines for individuals older than age 60 years has led to stagnating rates for age 50 to 59 years, despite corresponding advances in CRC treatment, and declines in risk factors such as smoking (Figure 3*A*).

Rectal Cancers Predominate Through Age 50 to 59 Years

Rectal and colon cancer incidence rates are increasing for ages 30 to 39 and 40 to 49 years (Supplementary Table 2). Notably, for age 50 to 59 years, rates of proximal colon, distal colon, and rectal cancer were similar in 1992, but rates of rectal cancer (APC, 0.7; 95% CI, 0.5–0.9) have since increased, whereas rates of proximal (APC, −0.3; 95% CI, −0.5 to −0.1) and distal (APC, −0.5; 95% CI, −0.7 to −0.3) colon cancer have slightly decreased (Figure 3*B*). Among 60- to 69-year-old individuals, rectal cancer exceeded distal colon cancer rates in 2008, although proximal colon cancer rates remain highest. Proximal colon, distal colon, and rectal cancer rates each started to more slowly decline in this age group starting in 2011. Proximal colon cancer rates decreased by 5.5% per year from 2008 to 2011 but decreasing incidence decelerated to about 2% per year from 2011 to 2019.

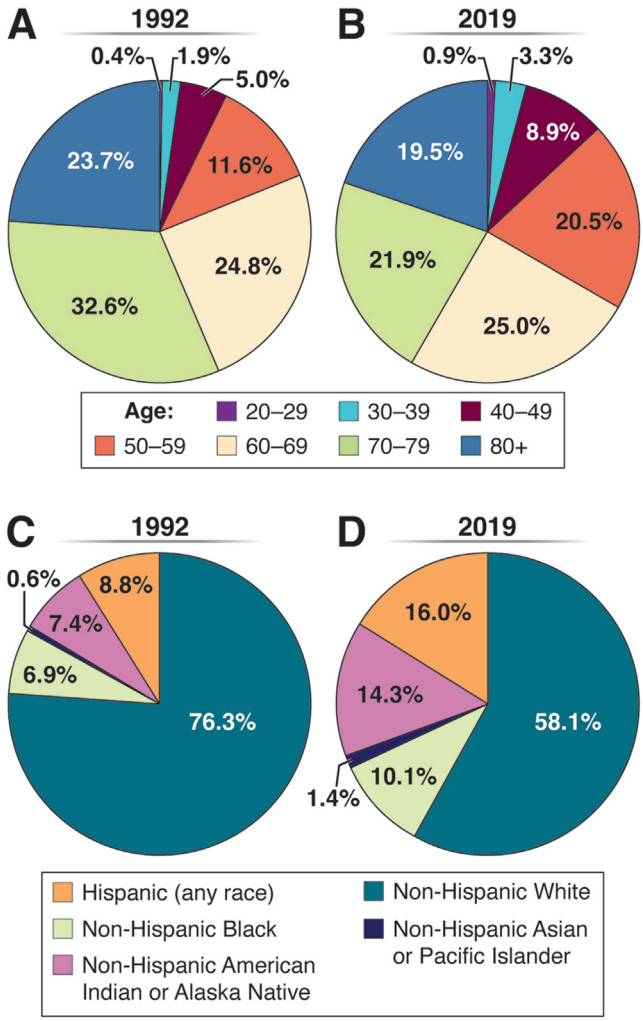

Figure 2. Distribution of CRC cases by age and race/ethnicity in 1992 vs 2019. Among CRC cases, distribution of age shifted to include more representation of individuals younger than age 60 between 1992 (*Panel A*) and 2019 (*Panel B*), and distribution of race/ethnicity shifted to include more representation of individuals from non-Hispanic Black, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaska Native, and Hispanic individuals between 1992 (*Panel C*) and 2019 (*Panel D*). Data are from the Surveillance Research Program, National Cancer Institute. SEER 12, 1992–2019. SEER, Surveillance, Epidemiology, and End Results

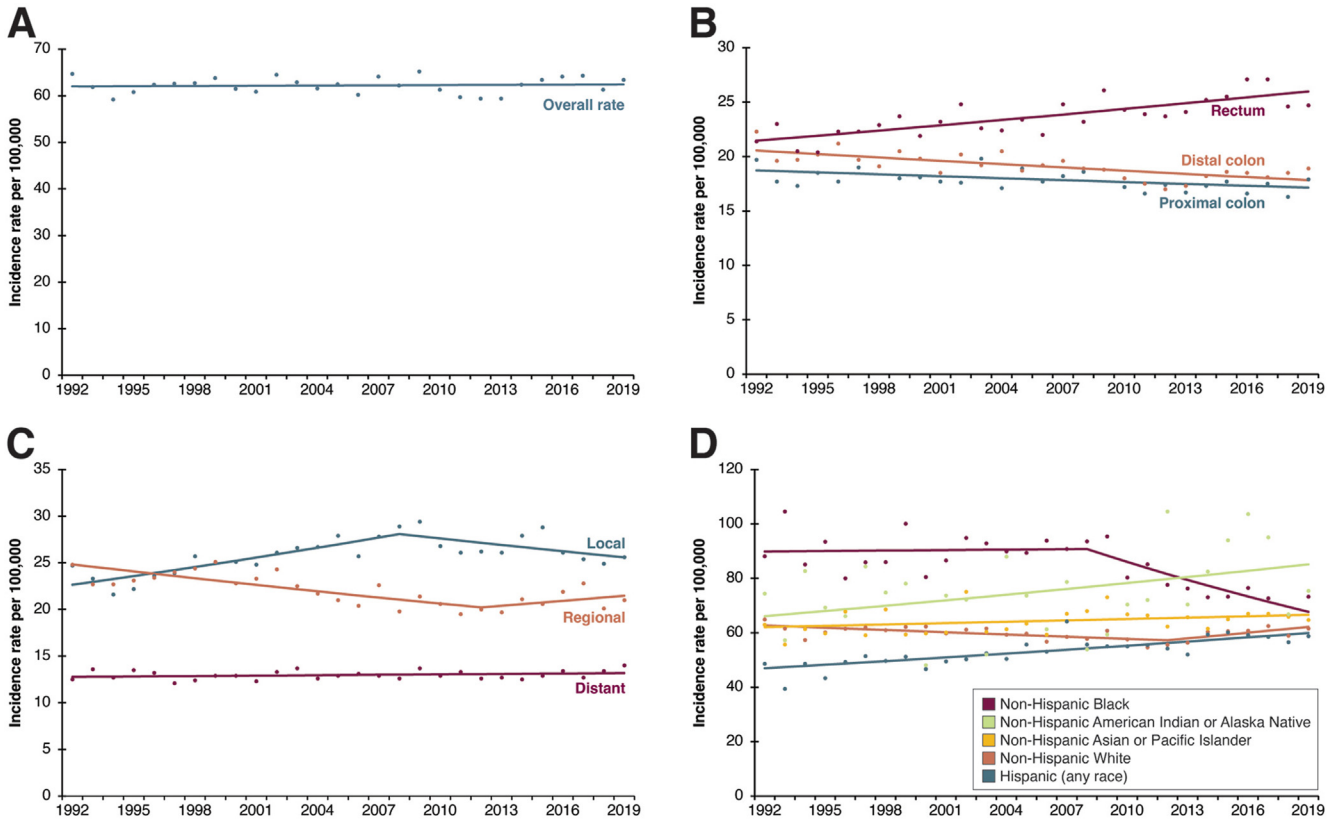

Figure 3. Modeled and observed incidence rates of CRC for age 50 to 59 years, overall (*A*) and by anatomic site (*B*), stage at diagnosis (*C*), and race and ethnicity (*D*). Modeled rate (*illustrated with smooth line*) estimated with joinpoint regression using Joinpoint Regression Program version 4.9.1 (Surveillance Research Program, National Cancer Institute). SEER 12, 1992–2019. Y-axis scale varied to illustrate trend. SEER, Surveillance, Epidemiology, and End Results

Rates of Distant Stage Disease Rapidly Increase and Slowly Decrease

Distant stage CRC has shown concerning trends since 1992 (Supplementary Table 3). For age 50 to 59 years, local (2008–2019: APC, −0.8; 95% CI, −1.6 to −0.1) and regional (1992–2012: APC, −1.0; 95% CI, −1.4 to −0.6) stage CRC have decreased over time, but distant stage rates (APC, 0.1; 95% CI, −0.1 to 0.3) have remained stagnant (Figure 3*C*). Distant stage rates have increased most rapidly for ages 30 to 39 (APC, 3.2; 95% CI, 2.7–3.7) and 40 to 49 (APC, 2.5; 95% CI, 2.2–2.8) years. For age 60 to 69 years, there have been slower declines in distant stage disease (1992–2019: APC, −1.9; 95% CI, −2.1 to −1.6) compared with local (2003–2019: APC, −3.9; 95% CI, −4.4 to −3.5) and regional (2000–2010: APC, −4.7; 95% CI, −5.9 to −3.5) stage, although regional stage rates have slowed in this age group since 2010 (APC, −1.8; 95% CI, −3.0 to −0.6). After 2002, distant stage rates have also decreased more slowly for age 70 to 79 years (APC, −3.1; 95% CI, −3.4 to −2.8). Changes in rates by stage could be due to emergence of more aggressive CRC biology but may also be explained by improvements in staging such as imaging.

Evolving Trends by Race and Ethnicity

Incidence rates of EOCRC have increased for all racial/ethnic groups since the early 1990s, but they vary in magnitude or slope (Supplementary Table 3). Rates have increased rapidly among non-Hispanic White (APC, 2.6; 95% CI, 2.4–2.9) and Hispanic (APC, 2.6; 95% CI, 2.2–3.1) individuals and more slowly among non-Hispanic Black (APC, 0.7; 95% CI, 0.3–1.0) and non-Hispanic API (APC, 0.4; 95% CI, 0.1–0.8) individuals. Rates remain highest among non-Hispanic AI/AN individuals. As a consequence, differences in incidence rates by race/ethnicity in 1992 have narrowed through 2019.

Whether increases in EOCRC by race/ethnicity will continue at older ages is unclear. For example, for age 50 to 59 years (Figure 3*D*), incidence rates have increased annually by about 1% among non-Hispanic White (APC, 1.2; 95% CI, 0.0–2.4) and Hispanic (APC, 0.9; 95% CI, 0.6–1.2) individuals but have decreased—although remain higher—among non-Hispanic Black individuals (APC, −2.6; 95% CI, −3.7 to −1.5). For ages 60 to 69 and 70 to 79 years, rates began to more slowly decrease among non-Hispanic White individuals in 2011 but have continued to steadily decrease in other racial and ethnic

groups. Across all age groups, the proportion of individuals diagnosed with CRC under age 60, and who are non-White has markedly increased (Figure 2).

Taken together, the combined impact of age-related increases in CRC and birth cohort-related trends are likely to result in substantial and important increases in the absolute number of people diagnosed with CRC, particularly among *Generation X* members now aging into their 50s and 60s.

Risk Factors, Potential Etiologies, and Mechanisms: Applying and Extending Lessons From EOCRC to Birth Cohort CRC

Few studies have examined CRC through the lens of birth cohort, which requires considering both age and birth year. Table 1 summarizes evidence on risk factors and etiology, hypothesized mechanisms, and relevance to EOCRC and birth cohort CRC, reviewed in additional detail below.

Birth cohort CRC, including increasing EOCRC incidence, is likely driven by a range of factors including demographic, lifestyle, early-life, environmental, genetic, and somatic factors, as well as interactions among these factors.[13] The mix of all exposures in a lifetime—beginning in utero at the time of conception through adulthood—can be represented in the concept of the exposome.[14] A conceptual model for suspected etiologies and mechanisms for birth cohort CRC is presented in Figure 4, and includes genetic factors, exposomal elements, and gene-environment interactions that lead to somatic changes implicated in the rise of EOCRC in the U.S. and globally. Our version is adapted from prior published visual representations of life-course exposures[15–17] and presents etiologic factors through the lens of birth cohort. It

Table 1. Risk Factors, Potential Etiologies, and Mechanisms for Birth Cohort CRC

Risk factors/etiology	Hypothesized mechanism	Relevance to birth cohort CRC
Race and ethnicity	Race and ethnicity likely a proxy for social determinants of health related to exposures, access to care	NHB and AI/AN individuals have the highest EOCRC rates historically, and rises in incidence have been highest in NHW and Hispanic individuals. Trends may extend beyond EOCRC because of increasing generational inequality, such as more income inequality and food insecurity in birth cohorts since Baby Boomers
Overweight/obesity Diabetes	Weight and metabolism may influence systemic inflammation, metabolic reprogramming, and adipose tissue-dependent effects and likely have effects on oxidative stress, DNA repair, microbiome, and immune function	Overweight/obesity, diabetes associated with EOCRC, and generational trends towards increasing body weight and diabetes may contribute to increased risk beyond early onset
Alcohol	Direct genotoxicity, increased reactive oxygen species, transcription factor activation, one-carbon metabolism, methylation and dysbiosis may all result from alcohol exposure	Alcohol is associated with EOCRC; it is unclear how generational trends in alcohol use may extend risk beyond risk for early onset CRC
Diet (sugar-sweetened beverages, processed meat, Western diet)	Reactive oxygen species, direct genotoxicity, dysbiosis, and inflammation secondary to less healthy diets may contribute to CRC pathogenesis	Less healthy dietary patterns have been associated with EOCRC, and adverse dietary patterns have generational trends that could portend persistent increased risk for CRC beyond early onset
Early life exposures (In utero exposure to maternal obesity or maternal pregnancy weight gain, and medications [eg, long-acting sulfonamides, 17α-hydroxyprogesterone caproate; Bendectin], increased birth weight, childhood obesity, high dairy intake)	Exposures during developmental windows of susceptibility may reprogram developing gastrointestinal tract or induce epigenetic and metabolic alteration that increase susceptibility	Influence of early life exposures associated with EOCRC on later onset CRC risk requires further study
Microbiome	Data have linked risk factors such as early life antibiotic exposure, less healthy diet, and obesity to dysbiosis	Life course impacts of dysbiosis on EOCRC and later onset CRC risk require further study

CRC, Colorectal cancer; EOCRC, early onset colorectal cancer; NHB, non-Hispanic Black; AI/AN, American Indian/Alaska Native; NHW, non-Hispanic White.

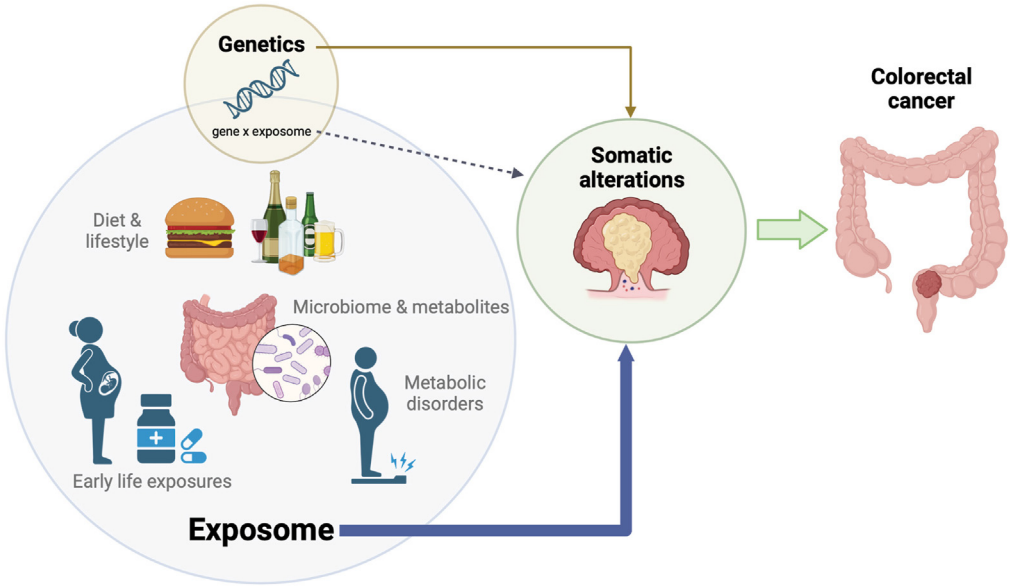

Figure 4. Conceptual framework for interaction between the exposomal and germline genetic factors on somatic alterations to determine CRC risk. Exposomal factors such as diet and lifestyle (eg, alcohol, Western diet), early-life exposures (eg, mode of delivery, antibiotics), metabolic disorders (eg, obesity, diabetes), and gut microbiome and metabolites are believed to initiate and/or promote somatic alterations leading to CRC. Germline genetic factors such as high-penetrance pathogenic variants (eg, mismatch repair genes in Lynch syndrome) and moderate- to low-penetrance variants (eg, single nucleotide polymorphisms) also drive somatic alterations and carcinogenesis. Based on current evidence, we postulate exposomal factors, possibly mediated through changes in the microbiome, play a larger role than germline genetics in driving somatic alterations and CRC risk, and that gene-by-exposome interactions likely modify somatic alterations and cancer development. *Figure created with BioRender.com*.

is likely colorectal carcinogenesis occurs through similar pathways regardless of age, and birth cohort CRC may be driven by a greater number, dose, and/or timing of high-risk exposures across the life course. Exposures may be mediated by a common factor such as metabolic derangement and/or alterations to the gut microbiome. However, mechanistic studies by birth cohort remain limited and are needed to support these hypotheses.

Demographic Risk Factors

Demographic risk factors associated with EOCRC include increasing age,[18–20] male sex,[19–21] and race and ethnicity.[20,22–25] As shown previously, White and Hispanic individuals in the U.S. have experienced a steeper increase in EOCRC incidence than API and non-Hispanic Black individuals, and non-Hispanic Black and AI/AN individuals continue to have the highest absolute incidence of EOCRC.[22,24,25] Historic differences in EOCRC incidence by race and ethnicity were likely the result of multiple factors, including variation in risk factor prevalence by race/ethnicity and differences in social determinants of health related to exposures, access to high-quality health care, and ability to utilize care. When viewed through the lens of birth cohort, demographic factors linked to EOCRC are expected to continue to be relevant. For example, we postulate narrowing of disparities, with rates for non-Black individuals converging towards rates among non-Hispanic Black individuals, representing increasing pervasiveness of adverse social determinants of health among non-Black individuals in more recent birth cohorts. Indeed, some key social determinants of health have been trending in an adverse direction: in the U.S., birth cohorts since *Baby Boomers* are experiencing increasing income inequality,[26] more food insecurity,[27] higher rates of disability and chronic disease as prior generations,[28] and persisting disparities in access to health care[29,30] in many regions.

Comorbidities

Comorbidities associated with EOCRC include metabolic conditions such as obesity, type 2 diabetes, and hyperlipidemia. Obesity, defined as body mass index (BMI) $\geq$30 kg/m^2 in most studies, is often cited as a major EOCRC risk factor and is associated with EOCRC in many U.S. and international studies.[20,21,31–40] Prior studies have identified an association between EOCRC and BMI for both overweight and obese thresholds as well as for weight gain after age 18.[20,36] A meta-analysis of 6 studies identified excess EOCRC risk among overweight ($\leq$55 years; BMI $\geq$25–29.9 kg/m^2; odds ratio [OR], 1.32; 95% CI, 1.19–1.47) and obese ($\leq$55 years; $\geq$30 kg/m^2; OR, 1.88; 95% CI, 1.40–2.54)[38] individuals compared with normal weight. A meta-analysis including 14 studies had consistent findings for obesity and EOCRC risk (relative risk [RR], 1.54; 95% CI, 1.01–2.35).[21] Of note, three of the included studies[19,22,41] identified an inverse relationship between

obesity and EOCRC risk, and others demonstrated a null relationship.[23,42] In at least one of these studies, the inverse relationship was likely attributable to weight loss as a symptom of CRC.[19] Metabolic syndrome (≥3 conditions among obesity, hypertension, hyperlipidemia, and hyperglycemia/type 2 diabetes) may elevate risk of EOCRC,[32] but this association requires further investigation.

There are also data supporting a role of elevated blood glucose or type 2 diabetes in EOCRC; however, evidence is also mixed for this association.[18,31,34,35,43–45] A meta-analysis demonstrated a pooled OR of 1.60 (95% CI, 1.32–1.95%) for 2 studies that evaluated the association between EOCRC and type 2 diabetes.[31,43,45] At least one published study did not identify an association.[42]

Hyperlipidemia (elevated cholesterol and/or triglycerides) is associated with EOCRC in a few studies, likely as a marker of metabolic disease burden. Three studies with considerable heterogeneity suggest elevated cholesterol and triglycerides increase EOCRC risk (pooled RR, 1.62; 95% CI, 1.22–2.13),[18,20,21,23] whereas another meta-analysis examining risk for early onset adenoma and CRC reported a pooled OR of 1.51 (95% CI, 1.41–1.62)[31,34,35,44,45] for elevated triglycerides. Additional comorbidities implicated in EOCRC risk include metabolic syndrome,[35,44,45] elevated blood pressure,[34,35,44,45] inflammatory bowel disease,[20] and chronic kidney disease,[20] although data are limited.

Birth cohort effects are apparent for many of the comorbidities associated with EOCRC. In particular, the past 40 years have seen increasing prevalence of elevated BMI, type 2 diabetes, metabolic disease, and hyperlipidemia by birth cohort.[46–48] Obesity and severe obesity are increasingly prevalent among individuals born in the 1950s, 1960s, 1970s, and 1980s (compared with the 1940s birth cohort).[49] Similar birth cohort effects have been implicated for type 2 diabetes.[50,51]

Potential Mechanisms of Comorbid Conditions on Changing CRC Epidemiology

Based on mechanistic studies, comorbid conditions appear to have biologic plausibility as contributors to changing epidemiology of CRC. For example, related to obesity and metabolism, mechanisms involve systemic inflammation, metabolic reprogramming, and adipose tissue-dependent effects as well as likely effects on oxidative stress, DNA repair, and microbiome and immune function, but are incompletely understood.[52] Mouse models have shown high fat diet-induced obesity augmented the number and function of intestinal stem cells through PPAR-d activation, leading to increased tumor initiation.[53] In addition, high-fat diet-induced obesity in mice altered the tumor microenvironment and anti-tumor immunity, which could be relevant for tumor progression and immunotherapy response.[54] Further, obesity hormones were noted to impact expression of inflammatory genes in a colon cancer cell line from a young adult.[55] Additional mechanistic studies are needed to better understand impact of obesity and metabolic dysregulation on birth cohort CRC, especially given birth cohort effects for rising prevalence of obesity and metabolic conditions.

Lifestyle and Dietary Risk Factors

Commonly reported lifestyle EOCRC risk factors include alcohol use, physical inactivity, tobacco use, and dietary patterns. Of these, an association with high alcohol consumption is the most consistent risk factor and strongest in magnitude.[20,42,56–58] In a meta-analysis of 14 studies, the pooled RR was 1.71 (95% CI, 1.62–1.80) for alcohol consumption with minimal heterogeneity and minimal evidence of publication bias.[20,21,42,57] Of note, other studies have found no association between alcohol intake and EOCRC risk,[22,33,58,59] and studies often employ very different definitions for heavy or excessive alcohol consumption.

For several lifestyle factors, existing data are mixed. There is evidence supporting a possible role for physical inactivity[60,61] and sedentary lifestyle[22,62] in EOCRC, but an almost equal weight of evidence against an association for these factors.[42,56,58,59] Tobacco consumption is associated with EOCRC risk in some studies[18,20,22,31,33–35,37,41,63] but not others.[19,56,57,59,64,65] In the aforementioned meta-analysis, cigarette smoking was not associated with EOCRC risk (pooled RR, 1.35; 95% CI, 0.81–2.25) with considerable heterogeneity among included studies.[18–21,37,57]

Dietary patterns, including consumption of sugar-sweetened beverages,[64,66,67] processed meat,[42,56] and Western diet (characterized as a modern diet of refined grains, high-fat dairy, processed meats, high-sugar beverages, lower fiber, and ultra-processed food content)[22,64,67] have been significantly associated with EOCRC.[58] Conversely, high intake of fish, B-carotene, vitamin C, folate, vitamin E, aspirin, vegetables, and fruit has been associated with reduced EOCRC risk.[19,42] Possible agricultural and occupational dietary additives involved in EOCRC pathogenesis include fillers, additives, chemicals, nitrates, synthetic dyes, high-fructose corn syrup, and organic dusts.[16,58]

Considering birth cohort CRC in context of lifestyle factors may be of special relevance because lifestyle trends are often a key defining characteristic of birth cohorts. Additionally, birth cohort effects might explain why research on lifestyle factors has shown mixed associations for some factors, and consistent associations for others. Studies examining associations between tobacco exposure and EOCRC could have been confounded by the distribution of birth year among cases and controls. As an example, primary and secondhand exposure to tobacco smoking has been decreasing over time.[68] If studies of tobacco smoking and EOCRC included cases and controls from a range of birth years (eg. a mix of

Baby Boomers, Generation X, and *Millennials*), the ability to detect an association with tobacco may be limited, especially if controls were drawn from birth cohorts differentially exposed to secondhand smoke. Moreover, many of the available data on EOCRC come from studies that have a large representation of individuals born before 1960, when birth cohort CRC trends began to be apparent.

Potential Mechanisms of Lifestyle and Dietary Factors on Changing CRC Epidemiology

Western diet, in particular, has been implicated in CRC carcinogenesis related to high-fat, low-fiber content, including a high amount of red and processed meats as well as refined sugars.[69] Pro-carcinogenic factors related to the Western diet include heme, arginine, N-nitroso compounds, heterocyclic amines, fatty acids, secondary bile acids, and polycylic aromatic hydrocarbons, among others, that mediate effects through pathways such as reactive oxygen species, direct genotoxicity, dysbiosis, and inflammation,[70] possibly modified by genetic variants. A missense variant in *HNF1A* among patients with EOCRC that, when introduced into a mouse model, showed increased colonic polyp formation with a high-fat diet due to activation of beta-catenin.[71] Low fiber content in Western diet is also an important risk factor for CRC. In a 2-week food exchange in African American and native African middle-age healthy participants, low fiber diet showed increased carcinogenic mucosal biomarkers as well as deleterious microbial and metabolic changes compared with a high fiber diet.[72]

Mechanisms of alcohol and colorectal carcinogenesis include direct genotoxicity, increase reactive oxygen species, transcription factor activation, one-carbon metabolism, methylation, and dysbiosis, among others.[73] Results from these and other studies underscore complexity and interrelatedness of the exposome and CRC risk that can be challenging to model and study using traditional experimental approaches.

Early-life Exposures and EOCRC

There is growing interest in the potential impact of early-life exposures on EOCRC risk, given the realization that adulthood exposures alone are unlikely to fully explain rising incidence. As life course begins at conception and includes gestation, infancy, childhood, and adolescence, exposures during these periods may also impact the likelihood of developing adenoma at a younger age. In utero exposure to maternal obesity or maternal pregnancy weight gain, medications such as long-acting sulfonamides, 17α-hydroxyprogesterone caproate for prevention of preterm birth, and the anti-nausea agent Bendectin (containing dicyclomine), and increased birth weight are associated with CRC risk in adult offspring, in studies that examined CRC in offspring through age 56 years.[74–77] In a population-based case-control study in Sweden, females born by cesarean delivery had significantly greater odds of EOCRC compared with females born via vaginal delivery.[9] Studies have also identified an association between CRC and childhood obesity (specific to EOCRC),[36,78] high vitamin A intake (CRC at age >50 years),[79] and high intake of dairy in childhood (CRC at age >50 years).[79] High intake of vegetables and vitamin A in adolescence are associated with lower CRC risk.[79] Overall, studies examining associations between early-life exposures and EOCRC are rare, and more research is warranted.

Convergence of birth cohort CRC and early-life exposures may result in continued increases in incidence and mortality. Early-life exposures have long-term consequences: infants and children exposed today will have that much higher of a risk of CRC as adults. Identifying early-life exposures associated with CRC has historically been challenging because of the long follow-up required in prospective studies, and issues of measurement error in retrospective studies. However, these challenges can now be addressed through pregnancy cohorts and population-based registries. For example, the Finnish Maternity Cohort[80] includes >1.5 million serum samples collected during pregnancy in the 1980s and can be linked with health and population registries to identify cancers diagnosed in now-adult offspring.

Role of Microbiome and Metabolites in Changing CRC Epidemiology

A common mechanism by which exposomal elements discussed previously could impact birth cohort CRC is through modulation of gut microbiome and its metabolites.[16] The gut microbiome interacts with many high-risk factors of the exposome (eg, diet, lifestyle, metabolic conditions), can change over time (as opposed to genetics, which are more fixed), and has been linked to CRC previously. Additionally, early-life exposures associated with EOCRC, including cesarean delivery and exposure to antibiotics, have separately been shown to result in early-life dysbiosis.[81]

Early evidence to support a role of microbial and metabolite alterations in EOCRC comes from a study that used metagenomic sequencing and metabolomic profiling to compare early- vs late-onset CRC and age-matched controls. Unique microbial features and metabolite markers in EOCRC were identified, several of which are linked to red meat and high-fat diets.[82] A study in mouse models of CRC showed high-fat diet promotes carcinogenesis through alterations of microbiome.[83] These and other studies provide intriguing evidence of a central role of gut dysbiosis in CRC including in younger adults, and additional work will be needed to dissect specific alterations by birth cohort, determine relationship to specific exposures, prove causality, and,

importantly, learn whether the gut microbiome could be leveraged to identify high-risk individuals and/or serve as targets for preventive interventions.

Germline Genetic Factors in Birth Cohort CRC

Germline genetic factors are important risk factors for CRC, especially in younger adults, but account for a smaller proportion of the overall population risk compared with the exposome, likely because genetic factors would not have changed significantly since the 1960s. Data on whether birth cohort effects influence penetrance of hereditary cancer syndromes and result in higher penetrance over successive birth cohorts are not available. Nevertheless, identification of at-risk individuals based on genetic variants associated with inherited syndromes enables earlier cancer screening and cascade testing in family members. Genetic testing in patients with CRC diagnosed under age 50 is recommended, with recent guidelines suggesting consideration of testing in all patients with CRC.[13,84] Prevalence of germline variants in EOCRC ranges between 14% and 25%: between 1 in 4 to 7 patients with EOCRC harbor a germline variant and are eligible for enhanced surveillance and family testing (Supplementary Table 5). Birth cohort effects might impact risk in inherited CRC syndromes, such as *PMS2*-associated Lynch syndrome,[85] although more studies are needed to understand whether changing epidemiology impacts individuals at baseline higher risk of CRC similar to the general population.

Impact of low- to moderate-penetrance germline genetic variants (ie, single nucleotide polymorphisms), in aggregate and individually associated with various exposures, has been evaluated in EOCRC. A large-scale study in European patients using 95 CRC variants from previous genome-wide association studies found that polygenic risk score had stronger association in early- vs late-onset CRC, and for patients with EOCRC was strongest in those without family history.[86]

Although birth cohort CRC is unlikely to be explained by changes in prevalence of low, moderate, and high-penetrance germline genetic variants, growing knowledge of variants associated with CRC has implications for birth cohort CRC, specifically with respect to potential gene-environment interactions for environmental factors that may be closely tied with birth cohorts. For example, individual genetic variants have been found to modify early onset neoplasia risk with specific exposures such as *HNF1A* with high-fat diet,[71] and *FUT2* with antibiotic use.[87] However, studies to date have not found polygenic risk score modifies environmental risks,[88,89] although larger studies are needed to evaluate gene-by-environment interactions. Gene-environment interactions for higher penetrance variants, such as Lynch syndrome, likely exist given variability in cancer risk by gene, sex, and continent, although more detailed studies are needed.[90]

Somatic Genetic Alterations in Changing CRC Epidemiology

Given that the exposome and germline genetic factors act directly or indirectly to initiate or propagate neoplasia through somatic alterations (Figure 4), it is attractive to ask whether prevalence of somatic changes differs by age of CRC onset to gain insights into potential unique carcinogenic mechanisms. Somatic alterations studied in EOCRC include microsatellite instability (MSI), somatic mutations, consensus molecular subtypes, and methylation. Results of these studies have not produced a singular, common somatic profile among EOCRC likely because of heterogeneity in study populations and methodologies. Moreover, most studies have evaluated somatic alterations by age of diagnosis rather than birth cohort, which could have resulted in mixed results.

MSI is one of the major carcinogenic pathways in CRC related to methylation or germline alterations in mismatch repair genes. MSI prevalence in EOCRC ranges from 3.8% to 21% with variability when comparing early- vs late-onset tumors, and most studies favoring a lower prevalence in EOCRC compared with older adults (Supplementary Table 6).

Somatic alterations have also been evaluated in EOCRC. Although most studies have shown decreased frequencies of *APC* and *BRAF* mutations, frequencies of *KRAS, TP53,* and other mutations have varied (Supplementary Table 7). Importantly, no significant differences in mutational profiles between early- and late-onset tumors were found when controlling for tumor sidedness,[91] highlighting potential confounding factors in previous analyses. Consensus molecular subtypes (CMS), derived from transcriptional profiles in tumors, show differences by age of diagnosis: CMS1 (MSI) was most common in individuals diagnosed under age 40, whereas CMS3 and 4 (metabolic and mesenchymal) were uncommon and CMS2 (canonical) was stable across age groups.

Methylation,[92] an important mechanism of tumor development in the colorectum,[93] has been evaluated in EOCRC. As measured by long-interspersed nucleotide elements, a continuum by age has been observed with lower frequency of methylation in EOCRC.[94] However, when measured with markers of accelerated aging, methylation has been associated with EOCRC,[95] suggesting premature aging of the colorectum as a potential mechanism. Methylation has also been associated with cortisol stress reactivity,[96] which could be a possible mechanistic link for increased cancer risk and social determinants of health that impact stress and cortisol levels.

Taken together, somatic alterations show possible differences by age of CRC diagnosis, though none have revealed the "smoking gun" that explains changes in CRC epidemiology. No studies have reported on prevalence of molecular subtypes through a birth cohort lens, and we postulate birth cohort differences in prevalence exist.

Future studies should consider somatic alterations in context of year of birth, specific exposures, social determinants of health, and, potentially, as biomarkers for CRC risk stratification, taking into consideration confounders such as tumor sidedness and stage that are unique features of birth cohort CRC.

Synthesis: Drawing Out Promising Clues From Potential Risk Factors, Etiologies, and Mechanisms

As described, existing evidence for EOCRC risk factors is highly variable and does not implicate a single etiology. Hofseth et al offer a unique and practical approach to disentangling what may be the key driving contributors to rising EOCRC incidence, highlighting several evidential and logical clues that, when met, may help explain why EOCRC incidence is increasing.[16] We have taken a similar approach in our synthesis of the data and present 5 clues for what might be contributing to the changing epidemiology of CRC, with additional consideration of birth cohort-related exposures, including factors associated with: (1) a birth cohort effect or temporal trend; (2) global presence; (3) rectal and distal colon cancers; (4) early-life exposure that persists during development to adulthood; and (5) convergence of historic sociodemographic differences. With regards to demographics, racial and ethnic differences in EOCRC incidence suggest that casual factors have variable prevalence or expression by race and ethnicity. The role of social determinants of health on exposome and EOCRC risk is less studied but may provide new insights into why CRC is occurring at younger ages and why racial and ethnic groups appear to be variably impacted. We consider risk factors meeting all 5 of these clues to be the current leading hypotheses for causes of EOCRC, and, by extension, for birth cohort CRC.

Table 2 lists commonly cited risk factors of EOCRC in the context of the 5 clues presented. Several exposures meet most or all the criteria, although there are likely many factors missing, and studies to explain causal mechanisms are needed. Of factors presented, there is existing evidence that obesity, physical inactivity/sedentary lifestyle, and processed/red meat fit all criteria. Other exposures like Western diet, sugar-sweetened beverages, alcohol, type 2 diabetes, hyperlipidemia, and elevated blood pressure also meet most criteria and suggest a strong dietary or metabolic etiology for EOCRC. Within the exposome, likely some or all of these elements interact with each other and with underlying genetic factors to elicit CRC, and we propose, especially for those exposures that vary by birth cohort, that these require further study as reasons for both EOCRC as well as larger birth cohort CRC trends.

Implications of Birth Cohort CRC for Research and Clinical Practice

Research Implications of Birth Cohort CRC

We postulate birth cohort CRC should influence our approach to conducting epidemiologic and translational

Table 2. Commonly Proposed Risk Factors for EOCRC and Relationship With 5 Major Causal Clues of Relevance to Birth Cohort CRC

Risk factor	Birth cohort effect or increasing temporal trend	Global presence	Distal colon and rectum	Present in early life	Varies by race and ethnicity
Metabolic comorbid conditions					
Obesity	√	√	?	√	√
Type 2 diabetes/metabolic disease	√	√	?	√	√
Hyperlipidemia	√	√	?	√	√
Elevated blood pressure	√	√	?	√	√
Physically inactive/sedentary lifestyle	√	√	√	√	√
Diet and lifestyle					
High alcohol consumption	?	√	√	X	√
Western diet	√	√	?	√	√
Sugar-sweetened beverages	√	√	?	√	√
Processed/red meat	√	√	√	√	√
Environmental and emerging factors					
PFAS and other environmental chemicals	√	√	?	√	√
Antibiotic exposure	√	√	?	√	√
Cesarean section	√	√	?	√	√

Note: √ indicates criteria fulfilled; X indicates criteria not fulfilled; ? indicates mixed or inadequate evidence.
Note: Adapted from Hofseth et al.[16]
CRC, Colorectal cancer; EOCRC, early onset colorectal cancer; PFAS, perfluoroalkyl and polyfluoroalkyl substances.

research evaluating risk factors and mechanisms of pathogenesis. When conducting epidemiologic analyses, or selecting biospecimens for translational research, we recommend including analyses grouping participants not just by age (eg, age $<$ vs $\geq$50 years at diagnosis) but also by birth cohort (eg, born before vs after 1960), and examining outcomes restricted to people born after 1960. Taking this approach may help elucidate characteristics specifically driven by birth cohort-related exposures that might be masked if patients with similar age at diagnosis but varying birth year are lumped together.

Accessing previously established and establishing new prospective cohorts with serial biospecimens will be needed to test new and established hypotheses as well as to develop approaches for early detection and prevention. Environmental chemicals introduced and/or increasingly used since the 1960s and implicated in other adult cancers should be closely scrutinized. For example, perfluoroalkyl and polyfluoroalkyl substances (PFASs)[97] are man-made fluorinated chemicals that were initially introduced in the U.S. in the 1940s,[98] and are now used in non-stick coatings, firefighting foams, and water-resistant products. PFAS exposure has been linked with hepatocellular carcinoma,[99] as well as predisposing conditions for CRC, such as ulcerative colitis.[100] Similarly, the role of social determinants of health resulting from generational socioeconomic trends has been understudied and could help understand changing CRC epidemiology.

Efficiently identifying risk factors and mechanisms may be improved by following the leads of the defining features of birth cohort CRC. Specifically, this could mean a more intense focus on rectal cancer, because its particular rise, including risk factors that may be more closely associated with rectal cancer pathogenesis. A focus on factors that are providing an early signal of association with EOCRC that have also been subject to cohort-related changes in prevalence could prove efficient. As an example, elevated BMI has been linked with increased risk for EOCRC,[9,15–20,22–26] and trends in obesity in the U.S have been increasing: focused research on high body weight over the life course and relationship to CRC among people born in 1960 and later could help elucidate extent to which elevated BMI could be contributing to increasing CRC.

Testing effects of the exposome on colorectal carcinogenesis is a formidable undertaking that will likely require application of conventional animal models and cell lines, and also patient-derived models such as organoids to evaluate diverse responses in humans, controlling for important confounders such as tumor sidedness and distant stage.

From a clinical research standpoint, several opportunities exist to extend prior work, particularly considering birth cohort (not just age at diagnosis) and including CRC cases from all ages. Risk-stratification models to date have largely utilized genetic, demographic, and clinical factors, have rarely undergone independent validation, and have shown low to moderate potential for risk stratification.[101] Validation of previously developed models and developing new models could be promising, particularly if biomarkers of risk, which might offer more precise stratification than genetic, demographic, and clinical factors alone, could be considered. Findings linking epidemiologic factors (such as alcohol and obesity) with CRC should help further justify interventions geared towards promoting healthy lifestyles. Additionally, given consequences among age-eligible individuals at risk for being unscreened appear to be becoming more adverse, the need for research on strategies to optimize screening participation and completion of all steps in the screening process appear to be more relevant than ever.

Clinical Implications of Birth Cohort CRC

The birth cohort effect of rising EOCRC incidence, increasing incidence among individuals aged 50 to 54 years, and flattening of prior decreasing incidence among individuals aged 55 to 74 years, and increasing rectal and distant stage diagnosis has several immediate clinical implications. For individuals under age 45, it remains critical to raise awareness of the need for timely workup of concerning signs and symptoms of CRC (such as hematochezia, iron deficiency anemia, and unintentional weight loss), and to measure and act on family history.[13,102] For individuals age 45 and older, given that disease burden appears to be increasing, we must redouble our efforts to address key quality shortfalls—essentially to make sure that what we already know works is being applied. Opportunities include renewing our commitment to optimizing screening participation and abnormal test follow-up, addressing disparities in screening participation (particularly by race/ethnicity, socioeconomic, and insurance status), and optimizing screening quality. Further, as the burden of CRC increases, it is ever more important to ensure every individual diagnosed with CRC has access to both guideline-appropriate care, and opportunity to consider innovative clinical trials. This may be particularly important for addressing increasing burden of rectal cancer, where treatment paradigms are rapidly evolving to favor more effective treatments such as neoadjuvant chemotherapy and radiation prior to surgery, and may soon include treatment options that may allow for less morbid treatments such as immunotherapy, including with the option of forgoing surgery altogether for some patients.[103]

Conclusion

CRC epidemiology is changing, consistent with a birth cohort effect. Risk factors, etiologies, and mechanisms to explain changing epidemiology require further study and will benefit from viewing the changing epidemiology through the lens of birth cohort—not just focusing on

EOCRC. Already, birth cohort CRC has major clinical implications, including increasing rectal cancer and distant stage disease across multiple age groups, and reversal of prior positive trends in incidence. These clinical implications underscore a need to raise awareness of importance of timely workup of red-flag signs and symptoms and measuring and acting on family history for individuals younger than 45 years, and redoubling efforts to ensure all age eligible individuals receive high-quality screening and follow-up. Recognizing the changing epidemiology of CRC as a birth cohort phenomenon will help us address the challenge of this concerning phenomenon.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.11.040.

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Correspondence
Address correspondence to: Samir Gupta, MD, MSCS, 3350 La Jolla Village Dr, MC 111D, San Diego, CA 92160. e-mail: s1gupta@health.ucsd.edu.

CRediT Authorship Contributions

Samir Gupta (Conceptualization; methodology; validation; investigation; resources; data curation; writing – original draft; writing – review and editing; visualization; supervision; project administration; funding acquisition)

Folasade P. May (Conceptualization; methodology; validation; investigation; resources; data curation; writing – original draft; writing – review and editing; visualization; supervision; project administration; funding acquisition)

Sonia S. Kupfer (Conceptualization; methodology; validation; investigation; resources; data curation; writing – original draft; writing – review and editing; visualization; supervision; project administration; funding acquisition)

Caitlin C. Murphy (Conceptualization; methodology; software; validation; formal analysis; investigation; resources; data curation; writing – original draft; writing – review and editing; visualization; supervision; project administration; funding acquisition)

Conflicts of interest

These authors disclose the following: Samir Gupta reports consulting for Geneoscopy, Guardant Health, Universal Diagnostics, InterVenn Bio, and CellMax. Caitlin C. Murphy reports consulting for Freenome. Folasade P. May reports consulting for Freenome, Exact Sciences, Medtronic, and Geneoscopy. The remaining author discloses no conflicts.

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Supplementary Table 1. APC in Age-specific Incidence Rates of CRC, SEER 12, 1992–2019

	Trend 1		Trend 2		Trend 3		Trend 4		Trend 5	
Age	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
All ages	1992–1995	−2.1 (−3.5 to −0.8)	1995–1998	1.6 (−1.2 to 4.5)	1998–2008	−2.2 (−2.4 to −1.9)	2008–2012	−3.8 (−5.3 to −2.3)	2012–2019	−1.3 (−1.7 to −0.9)
<50	1992–2013	1.9 (1.6–2.2)	2013–2019	3.1 (1.5–4.7)						
≥50	1992–1995	−2.1 (−3.4 to −0.9)	1995–1998	1.4 (−1.0 to 3.9)	1998–2008	−2.5 (−2.7 to −2.3)	2008–2012	−4.6 (−5.8 to −3.3)	2012–2019	−2.0 (−2.4 to −1.7)
30–39	1992–2019	2.6 (2.3–3.0)								
40–49	1992–2019	1.7 (1.5–1.9)								
50–59	1992–2019	0.0 (−0.1 to 0.2)								
60–69	1992–2000	−0.5 (−1.0 to 0.1)	2000–2008	−3.0 (−3.7 to −2.3)	2008–2011	−5.2 (−9.9 to −0.1)	2011–2019	−1.7 (−2.3 to −1.2)		
70–79	1992–1995	−3.0 (−5.1 to −1.0)	1995–1998	1.6 (−2.6 to 6.1)	1998–2008	−2.8 (−3.2 to −2.4)	2008–2013	−5.8 (−7.3 to −4.2)	2013–2019	−3.6 (−4.4 to −2.7)

Note: For each age group, we used Joinpoint Regression Program version 4.9.1.0 (Surveillance Research Program, NCI) to fit a series of joined lines to observed incidence rates (maximum 4 joinpoints), whereby the slope of the line segments is equivalent to the APC.
APC, Annual percent change; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

Supplementary Table 2. APC in Age-specific Incidence Rates of CRC by Anatomic Subsite, SEER 12, 1992–2019

	Trend 1		Trend 2		Trend 3		Trend 4		Trend 5	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Proximal colon										
All ages	1992–1999	0.7 (0.2–1.2)	1999–2008	−1.8 (−2.1 to −1.4)	2008–2011	−4.7 (−8.0 to −1.2)	2011–2019	−1.8 (−2.2 to −1.4)		
<50	1992–1995	−5.3 (−10.9 to 0.8)	1995–2005	2.4 (1.3–3.5)	2005–2008	−4.7 (−14.9 to 6.8)	2008–2017	5.9 (4.4–7.4)	2017–2019	−2.9 (−16.7 to 13.3)
≥50	1992–1999	0.7 (0.2–1.2)	1999–2008	−1.9 (−2.3 to −1.5)	2008–2011	−5.2 (−8.6 to −1.5)	2011–2019	−2.6 (−3.0 to −2.2)		
30–39	1992–2010	0.9 (−0.0 to 1.9)	2010–2019	7.5 (5.6–9.4)						
40–49	1992–1996	−3.9 (−8.3 to 0.7)	1996–2005	2.7 (1.3–4.1)	2005–2008	−4.8 (−15.8 to 7.6)	2008–2017	4.2 (2.8–5.6)	2017–2019	−6.8 (−18.4 to 6.5)
50–59	1992–2019	−0.3 (−0.5 to −0.1)								
60–69	1992–2000	0.7 (−0.0 to 1.5)	2000–2008	−2.1 (−3.0 to −1.2)	2008–2011	−5.5 (−11.3 to 0.7)	2011–2019	−1.9 (−2.6 to −1.3)		
70–79	1992–1999	0.7 (−0.3 to 1.6)	1999–2008	−2.0 (−2.8 to −1.2)	2008–2019	−4.4 (−4.8 to −3.9)				
Distal colon										
All ages	1992–1994	−4.3 (−8.9 to 0.6)	1994–1998	−0.5 (−2.7 to 1.8)	1998–2007	−2.8 (−3.4 to −2.3)	2007–2012	−4.9 (−6.5 to −3.3)	2012–2019	−1.9 (−2.6 to −1.1)
<50	1992–2019	1.4 (1.1–1.8)								
≥50	1992–1994	−4.8 (−9.2 to −0.3)	1994–1998	−0.6 (−2.8 to 1.7)	1998–2008	−3.3 (−3.7 to −2.9)	2008–2011	−7.0 (−11.9 to −1.8)	2011–2019	−2.9 (−3.5 to −2.4)
30–39	1992–2019	2.5 (1.9–3.1)								
40–49	1992–2019	1.4 (1.0–1.7)								
50–59	1992–2019	−0.5 (−0.7 to −0.3)								
60–69	1992–2007	−2.6 (−3.1 to −2.1)	2007–2012	−7.0 (−10.7 to −3.1)	2012–2019	−2.3 (−4.1 to −0.6)				
70–79	1992–2003	−2.4 (−3.0 to −1.9)	2003–2019	−5.9 (−6.3 to −5.5)						
Rectum										
All ages	1992–1995	−2.5 (−5.1 to 0.2)	1995–1998	2.3 (−3.1 to 8.0)	1998–2013	−2.1 (−2.3 to −1.8)	2013–2019	−0.4 (−1.2 to 0.5)		
<50	1992–2019	2.6 (2.3–2.9)								
≥50	1992–1995	−2.5 (−5.4 to 0.5)	1995–1998	1.5 (−4.7 to 8.0)	1998–2009	−2.5 (−2.9 to −2.0)	2009–2012	−3.9 (−9.9 to 2.4)	2012–2019	−1.0 (−1.8 to −0.2)
30–39	1992–2019	2.9 (2.3–3.4)								
40–49	1992–2019	2.2 (1.9–2.6)								
50–59	1992–2019	0.7 (0.5–0.9)								
60–69	1992–1999	−0.1 (−1.4 to 1.1)	1999–2011	−3.2 (−3.8 to −2.5)	2011–2019	−0.9 (−1.8 to 0.1)				
70–79	1992–2008	−2.1 (−2.6 to −1.6)	2008–2012	−8.2 (−15.1 to −0.8)	2012–2019	−2.1 (−4.2 to −0.0)				

Note: For each age group, we used Joinpoint Regression Program version 4.9.1.0 (Surveillance Research Program, NCI) to fit a series of joined lines to observed incidence rates (maximum 4 joinpoints), whereby the slope of the line segments is equivalent to the APC; anatomic subsite defined as proximal colon (ascending colon, hepatic flexure, transverse colon), distal colon (splenic flexure, descending colon, sigmoid colon), and rectum (rectosigmoid junction, rectum)
APC, Annual percent change; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

Supplementary Table 3. APC in Age-specific Incidence Rates of CRC by Stage at Diagnosis, SEER 12, 1992–2019

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC (95% CI)	Year	APC (95% CI)	Years	APC (95% CI)		
Local								
All ages	1992–1995	−2.7 (−6.0 to 0.7)	1995–1998	3.5 (−3.5 to 10.9)	1998–2008	−1.5 (−2.0 to −0.9)	2008–2019	−4.0 (−4.4 to −3.6)
<50	1992–1994	−8.3 (−17.4 to 1.8)	1994–1997	8.8 (−2.4 to 21.2)	1997–2019	1.7 (1.4–2.0)		
≥50	1992–1999	0.5 (−0.6 to 1.7)	1999–2008	−1.6 (−2.5 to −0.8)	2008–2019	−4.7 (−5.2 to −4.1)		
30–39	1992–2019	3.0 (2.4–3.5)						
40–49	1992–2006	2.7 (1.9–3.6)	2006–2019	0.1 (−0.6 to 0.9)				
50–59	1992–2008	1.4 (0.8–1.9)	2008–2019	−0.8 (−1.6 to −0.1)				
60–69	1992–2003	−0.1 (−0.9 to 0.8)	2003–2019	−3.9 (−4.4 to −3.5)				
70–79	1992–2001	−0.2 (−1.0 to 0.6)	2001–2008	−2.1 (−3.6 to −0.6)	2008–2019	−6.5 (−7.1 to −5.8)		
Regional								
All ages	1992–1996	−1.5 (−4.0 to 1.1)	1996–1999	3.2 (−4.7 to 11.7)	1999–2012	−3.6 (−4.0 to −3.1)	2012–2019	−1.1 (−2.1 to 0.0)
<50	1992–2019	2.0 (1.7–2.2)						
≥50	1992–1996	−1.5 (−4.0 to 1.1)	1996–1999	3.2 (−4.3 to 11.4)	1999–2012	−4.1 (−4.5 to −3.6)	2012–2019	−2.0 (−3.1 to −0.9)
30–39	1992–2019	2.6 (2.1–3.0)						
40–49	1992–2019	1.6 (1.3–1.9)						
50–59	1992–2012	−1.0 (−1.4 to −0.6)	2012–2019	0.9 (−0.9 to 2.6)				
60–69	1992–2000	0.4 (−1.1 to 1.9)	2000–2010	−4.7 (−5.9 to −3.5)	2010–2019	−1.8 (−3.0 to −0.6)		
70–79	1992–2000	−0.0 (−1.2 to 1.2)	2000–2019	−4.5 (−4.8 to −4.1)				
Distant								
All ages	1992–2000	−0.6 (−1.3 to 0.1)	2000–2019	−1.4 (−1.6 to −1.2)				
<50	1992–2019	2.6 (2.3–2.9)						
≥50	1992–2002	−1.0 (−1.4 to −0.6)	2002–2017	−2.2 (−2.5 to −2.0)	2017–2019	1.2 (−3.7 to 6.3)		
30–39	1992–2019	3.2 (2.7–3.7)						
40–49	1992–2019	2.5 (2.2–2.8)						
50–59	1992–2019	0.1 (−0.1 to 0.3)						
60–69	1992–2019	−1.9 (−2.1 to −1.6)						
70–79	1992–2002	−1.2 (−1.9 to −0.6)	2002–2019	−3.1 (−3.4 to −2.8)				

Note: For each 10-year age group, we used Joinpoint Regression Program version 4.9.1.0 (Surveillance Research Program, NCI) to fit a series of joined lines to observed incidence rates (maximum 4 joinpoints), whereby the slope of the line segments is equivalent to the APC; stage at diagnosis defined as local, regional, and distant using SEER Summary Stage 1977, SEER Summary Stage 2000, and SEER Summary Stage 2018.
APC, Annual percent change; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

Supplementary Table 4. APC in Age-specific Incidence Rates of CRC by Race and Ethnicity, SEER 12, 1992–2019

	Trend 1		Trend 2		Trend 3		Trend 4		Trend 5	
	Years	APC (95% CI)	Year	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
NH Asian										
All ages	1992–2002	−0.4 (−1.0 to 0.2)	2002–2019	−2.5 (−2.7 to −2.3)						
<50	1992–2019	0.4 (0.1–0.8)								
≥50	1992–2002	−0.5 (−1.2 to 0.1)	2002–2019	−2.9 (−3.1 to −2.6)						
30–39	1992–2019	−0.3 (−1.1 to 0.5)								
40–49	1992–2019	0.6 (0.2–1.0)								
50–59	1992–2019	0.3 (−0.1 to 0.6)								
60–69	1992–2010	−1.2 (−1.7 to −0.7)	2010–2019	−3.1 (−4.3 to −1.8)						
70–79	1992–1995	−7.7 (−14.5 to −0.4)	1995–2002	1.0 (−1.4 to 3.4)	2002–2019	−4.5 (−5.0 to −4.1)				
NH AIAN										
All ages	1992–2019	0.2 (−0.2 to 0.6)								
<50	1992–2019	3.6 (2.2–5.1)								
≥50	1992–2019	−0.3 (−0.7 to 0.1)								
30–39	1992–2019	3.3 (1.0–5.5)								
40–49	1992–2019	3.5 (1.8–5.2)								
50–59	1992–2019	0.9 (0.0–1.9)								
60–69	1992–2019	−0.5 (−1.3 to 0.3)								
70–79	1992–2019	−0.7 (−1.5 to 0.0)								
NH Black										
All ages	1992–2007	−0.5 (−0.9 to −0.2)	2007–2014	−4.5 (−5.7 to −3.2)	2014–2019	−1.2 (−2.8 to 0.4)				
<50	1992–2019	0.7 (0.3–1.0)								
≥50	1992–2007	−0.6 (−1.0 to −0.3)	2007–2015	−4.9 (−5.9 to −3.9)	2015–2019	−0.8 (−3.2 to 1.6)				
30–39	1992–2019	1.6 (1.0–2.3)								
40–49	1992–2019	0.3 (−0.1 to 0.8)								
50–59	1992–2008	0.1 (−0.7 to 0.8)	2008–2019	−2.6 (−3.7 to −1.5)						

Supplementary Table 4. Continued

	Trend 1		Trend 2		Trend 3		Trend 4		Trend 5	
	Years	APC (95% CI)	Year	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
60–69	1992–2003	0.2 (−1.1 to 1.6)	2003–2019	−3.0 (−3.6 to −2.3)						
70–79	1992–2006	−0.9 (−1.9 to 0.1)	2006–2019	−4.4 (−5.5 to −3.3)						
30–39	1992–2019	1.6 (1.0–2.3)								
Hispanic										
All ages	1992–2007	0.0 (−0.4 to 0.4)	2007–2013	−2.9 (−4.5 to −1.2)	2013–2017	0.8 (−2.8 to 4.5)	2017–2019	−4.1 (−10.5 to 2.7)		
<50	1992–2019	2.6 (2.2–3.1)								
≥50	1992–1998	1.1 (−0.5 to 2.7)	1998–2008	−0.8 (−1.5 to −0.1)	2008–2013	−3.3 (−5.4 to −1.1)	2013–2017	−0.2 (−3.4 to 3.1)	2017–2019	−5.1 (−10.8 to 1.0)
30–39	1992–2019	3.7 (3.0–4.3)								
40–49	1992–2019	2.2 (1.7 to 2.7)								
50–59	1992–2019	0.9 (0.6–1.2)								
60–69	1992–2019	−1.2 (−1.5 to −0.9)								
70–79	1992–2004	0.1 (−0.8 to 1.1)	2004–2019	−3.1 (−3.7 to −2.5)						
NH White										
All ages	1992–1995	−2.3 (−3.5 to −1.0)	1995–1998	1.8 (−0.9 to 4.6)	1998–2008	−2.5 (−2.7 to −2.2)	2008–2011	−4.7 (−7.6 to −1.7)	2011–2019	−1.3 (−1.6 to −0.9)
<50	1992–2019	2.6 (2.4–2.9)								
≥50	1992–1995	−2.3 (−3.5 to −1.0)	1995–1998	1.6 (−1.0 to 4.3)	1998–2008	−2.8 (−3.1 to −2.6)	2008–2011	−5.7 (−8.4 to −2.9)	2011–2019	−2.1 (−2.4 to −1.8)
30–39	1992–2019	3.4 (3.0–3.8)								
40–49	1992–2019	2.2 (2.0–2.5)								
50–59	1992–2012	−0.5 (−0.7 to −0.2)	2012–2019	1.2 (0.0–2.4)						
60–69	1992–2000	−0.5 (−1.2 to 0.1)	2000–2008	−3.7 (−4.5 to −3.0)	2008–2011	−6.8 (−12.4 to −0.7)	2011–2019	−1.7 (−2.4 to −1.0)		
70–79	1992–1995	−2.5 (−4.8 to −0.2)	1995–1998	1.6 (−3.0 to 6.4)	1998–2008	−3.0 (−3.4 to −2.5)	2008–2011	−7.1 (−12.5 to −1.5)	2011–2019	−4.1 (−4.8 to −3.5)

Note: For each 10-year age group, we used Joinpoint Regression Program version 4.9.1.0 (Surveillance Research Program, NCI) to fit a series of joined lines to observed incidence rates (maximum 4 joinpoints), whereby the slope of the line segments is equivalent to the APC; racial and ethnic groups include: Hispanic (any race), non-Hispanic American Indian or Alaska Native, non-Hispanic Asian or Pacific Islander, non-Hispanic Black, and non-Hispanic White

APC, Annual percent change; CI, confidence interval; NH, non-Hispanic; SEER, Surveillance, Epidemiology, and End Results.

Supplementary Table 5. Prevalence of Germline Genetic Pathogenic Variants in Patients With EOCRC

Study	Cohort (<50 years)	Number of cancer genes tested	Pathogenic variant prevalence, %
Mork et al[104]	193 patients ≤35 years	Per genetic counselor	23
Yurgelun et al[105]	336 patients	25	14
Pearlman et al[106]	450 patients	25	16
Stoffel et al[107]	430 patients	67–124	25
Uson et al[108]	124 patients	83–84	22
Toh et al[109]	88 patients	64 genes (Lynch genes not included)	14
You et al[110]	130 patients	47	19
Cercek et al[91]	759 patients	76–88	17.5

Note: Adapted from Patel S et al.[25]
EOCRC, Early-onset colorectal cancer.

Supplementary Table 6. Prevalence of MSI-H tumors among EOCRC cases compared with LOCRC

Study (year)	Cohort	Rate of MSI-H in EOCRC (vs LOCRC)
Pearlman et al[106] (2017)	450 tumors Ohio	11%
Stoffel et al[107] (2018)	430 tumors U Michigan	9.5%
Willauer et al[92] (2019)	1525 metastatic tumors MD Anderson	6% (vs. 3%)
Cercek et al[91] (2022)	759 tumors MSKCC	6% (vs. 9%)
Ugai et al[111] (2023)	3089 tumors GECCO consortium	21% (vs. 16%)
Myer et al[112] (2023)	8044 tumors F1 somatic testing	3.8%

EOCRC, Early onset colorectal cancer; F1, Foundation One; LOCRC, late onset colorectal cancer; MSKCC, Memorial Sloan Kettering Cancer Center; MSI-H, microsatellite instability high.

Supplementary Table 7. Somatic mutations reported in EOCRC compared with LOCRC

Study (year)	Cohort	Somatic mutations in EOCRC vs LOCRC
Lieu et al[113] (2019)	1420 tumors (<40); MSS	↓ *APC*, *KRAS*, *BRAF*, *FAM123B* ↑ *TP53*, *CTNNB1*
Willauer et al[92] (2019)	634 metastatic tumors	↓ *APC*, *KRAS*, *BRAF* no difference *TP53*
Cercek et al[91] (2022)	730 MSS tumors	No differences when controlling for sidedness
Ugai et al[111] (2023)	3089 all tumors	↓ CIMP-H & *BRAF*
Holowatyj et al[114] (2023)	1832 non-hypermutated tumors	↓ mutation rate ↑ *TP53*, *LRP1B*, *TCF7L2* differences by race & ethnicity
Myer et al[112] (2023)	8044 tumors	↓ *APC* ↑ *KRAS* & *MAPK* pathway

Note: Underlined genes show variable patterns across studies.
EOCRC, Early onset colorectal cancer; LOCRC, late onset colorectal cancer; MSS, microsatellite stable.