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Rising incidence of early-onset colorectal cancer: a call for action

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Use of standardized official symbols: We use HUGO (Human Genome Organisation)-approved official symbols (or root symbols) for genes and gene products, including APC, ATM, BRAF, BRCA1, BRCA2, CDKN2A, CHECK2, CTNNB1, KRAS, MAPK, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, SMAD4, and TP53; all of which are described at www.genenames.org. Gene symbols are italicized whereas symbols for gene products are not italicized.

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Abstract

Early-onset colorectal cancer (CRC), which occurs in individuals under 50 years of age, has been increasing worldwide, especially in high-income countries, for unknown reasons. Plausible hypotheses for this rise include exposure to potential risk factors such as western-style diet, obesity, physical inactivity, and increased antibiotic use, especially in early life from prenatal to adolescent periods. These exposures may not only cause genetic and epigenetic alterations in colorectal epithelial cells, but also affect the gut microbiota and host immunity. When compared to later-onset CRCs, early-onset CRCs exhibit differential clinical, pathological, and molecular features. While certain existing resources can be utilized to elucidate the etiology of early-onset CRC and inform the development of effective prevention, early detection, and therapeutic strategies, there is a need for additional life-course cohort studies spanning the periods of early-life to young adulthood integrated with prospective biospecimen collections, omics biomarker analyses, and the molecular pathological epidemiology approach.

Introduction

Colorectal cancer (CRC) most often affects elderly individuals[1]. While overall CRC incidence rates have remained stable or declined in many high-income countries, incidence of early-onset CRC (generally defined as CRC diagnosed before the age of 50 years) has recently been increasing worldwide[2,3]. In this article, contrasting with “early-onset CRC”, we use the term “later-onset CRC” in patients aged 50 years or above. The reasons underlying this rise of early-onset CRC are poorly understood. This article discusses the current evidence for salient characteristics of early-onset CRC and its potential etiological mechanisms. A better understanding of the characteristics and etiology of early-onset CRC can promote effective prevention, early detection, and treatment strategies.

While we discuss differences in epidemiological, clinical, pathological, and molecular features between early-onset and later-onset CRC, there may not be a sharp dichotomy of the features in CRC patients aged 49 vs. those aged 50. Those characteristics of CRC may change in any way, with increasing age at diagnosis as well as changes in other key variables such as tumor location. Accordingly, we need to consider heterogeneity within early-onset CRC patients and within later-onset CRC patients.

What is already known?

Epidemiology

CRC is the third most common cancer worldwide with 1.8 million new cases and the second most common cause of cancer death with over 880,000 deaths in 2018[4]. CRC incidence varies substantially across continents[5,6] with the highest in Australia/New Zealand and the lowest in Africa and South-Central Asia[4]. These differences may be attributable to variations in genetic susceptibility, socioeconomic status, environmental exposures, diets, other lifestyle factors, and/or screening practices[7,8]. For the past two decades, CRC incidence has remained stable or declined in high-income countries, while low/middle-income countries with historically lower CRC rates have documented an increase in CRC incidence[5]. Established CRC risk factors include (but are not limited to) red and processed meat, alcohol, obesity, inflammatory bowel disease (IBD), CRC family history, and CRC-predisposing genetic variants, whereas protective factors include aspirin use, high systemic vitamin D level, high folate intake, and physical activity[8].

In recent decades, early-onset CRC incidence has been increasing in both men and women across many countries[2,9-11]. The average annual percent changes in early-onset CRC incidence were 4.0% in New Zealand, 2.8% in Canada and Australia, and 2.2% in the U.S. during 2008-2012[2]. In the U.S., early-onset CRC incidence has been increasing since the mid 1990s[12], and the age-adjusted early-onset CRC incidence per 100,000 persons was 5.9 cases in 2000 and 8.4 cases in 2017. Increases in early-onset CRC have also been documented in most European countries. Early-onset CRC incidence (per 100,000 persons) increased from 0.8 to 2.3 cases in individuals aged 20-29 years during1990-2016, from 2.8 to 6.4 cases in those aged 30-39 during 2006-2016, and from 15.5 to 19.2 cases in those aged 40-49 during 2005-2016. The average annual percent changes in early-onset CRC incidence were 7.9% in individuals aged 20-29, 4.9% in those aged 30-39, and 1.6% in those aged 40-49 during 2004-2016[3]. Taken together, early-onset CRC now represents a significant cancer burden among younger adults.

The increase of early-onset CRC incidence in the U.S. was initially largely driven by rectal cancer[12]. The annual percent change of rectal cancer incidence was 3.2% for ages 20-39 during 1980-2013, and 2.3% for ages 40-49 during 1991-2013, while that of colon cancer incidence was 2.4% for ages 20-29 during 1983-2013, 1.0% for ages 30-39 during 1988-2013, and 1.3% for ages 40-49 during 1996-2013[12]. Since 2012 early-onset CRC incidence has increased similarly for colon and rectum with the annual percent change of approximately 1.8%[1]. The rise in early-onset CRC incidence appeared more prominent for colon cancer than for rectal cancer in Europe[3].

The upward trend of early-onset CRC incidence in most western countries since the 1980s[3,12-15] seems to reflect a birth cohort effect, which means that temporal changes in certain risk factors might have differentially affected each age-group (i.e., birth cohort) with increased risk being carried forward to later time. There is a possibility that the observed birth cohort effect might be caused by secular trends in risk factor exposures during early life, typically referring to prenatal to adolescent life (in contrast to adulthood), and their delayed effects on CRC incidence[12,16]. Considering that the rise in CRC incidence has

generally followed the westernization of lifestyle, early-onset CRC will likely become an emerging issue in regions where western lifestyle had not been widely adopted until recently. Indeed, increasing incidence of early-onset CRC has already been documented in Taiwan, Korea, Japan, and Hong Kong[17]. Moreover, incidence of early-onset cancers of other body sites that share risk factors with CRC may also increase[18,19].

Most epidemiological investigations that examined potential risk factors for early-onset CRC were case-control studies[20-22], while relatively few studies prospectively examined exposure data collected before CRC diagnosis[23,24] (Table 1). Potential early-onset CRC risk factors shown in the case-control studies include male sex[21], race (black and Asian ethnicities)[21], family history of CRC[20,21], alcohol[20], weight loss of ≥5 kg (within five-year period preceding colonoscopy)[22], processed meat intake[20], and inflammatory bowel disease (IBD)[21]. On the contrary, aspirin use[22] and higher intake of vegetables[20], citrus fruits[20], fish[20], β-carotene[20], vitamin C[20], vitamin E[20], and folate[20] have been associated with lower risk of early-onset CRC[20,22]. In the two published prospective studies, sedentary lifestyle (measured as TV watching time)[23] and obesity[24] were associated with higher incidence of early-onset CRC. However, the association between obesity and early-onset CRC remains inconclusive with some studies showing positive associations[18,24] and another showing opposite results[22].

Certain socioeconomic factors, such as race/ethnicity, household income, education levels, and rural vs urban residence, have been associated with increased CRC incidence or mortality[25]. While African Americans have exhibited a relatively high but stable incidence of early-onset CRC, non-Hispanic whites have experienced a sharp increase in early-onset CRC incidence[2,26]. African American children and adolescents have relatively high prevalence of obesity and type 2 diabetes[27,28]. Nonetheless, it remains unclear why whites have shown such a rapid increase in early-onset CRC incidence but African Americans have not[1,26]. In terms of prognosis, African Americans have been associated with higher mortality compared to whites among early-onset CRC patients, and this difference appears to be attenuated among later-onset CRC patients[29].

In general, case-control studies sample hospital-based controls or colonoscopy controls, neither of which were random samples from the general population. There are likely differences in background populations that have given rise to cases vs. controls in case-control studies. Furthermore, differential recall between cases and controls remain an intractable problem when exposure data in cases (but not controls) are recalled after CRC diagnosis. Another issue in any study design is a reverse causation, as their underlying illness even before clinical detection may affect exposure data through changes in physical well-being, appetite, weight, etc. To address the reverse causation problem, data on exposures should ideally be collected long (years to decades) before CRC diagnosis.

Clinical features

Early-onset CRCs most commonly occur in the rectum (35-37%), followed by distal colon (25-26%) and proximal colon (22-23%)[1,30], while approximately 29%, 27% and 29% of CRCs diagnosed in individuals aged ≥50 years (hereafter referred to as later-onset CRCs) occur in rectum, distal colon, and proximal colon, respectively[30]. Certain risk factor

associations with later-onset CRC and their effect sizes appear to differ by anatomic sites[31]. For instance, BMI and waist circumference showed stronger associations with colon cancer compared to rectal cancer, and the associations of height and physical inactivity appeared confined to colon cancer[31]. In contrast, smoking presented a stronger association with rectal cancer in comparison to colon cancer[31]. However, it remains unclear whether these differences persist for colon and rectal cancer diagnosed under age 50. Considering the steep rise of early-onset rectal cancer compared to early-onset colon cancer incidence, epidemiological analyses stratified by colorectal subsites should be conducted[31].

Patients with early-onset CRC were more likely to be diagnosed at advanced stage (stage III-IV) compared to patients with later-onset CRC[32-34]. Early-onset CRC patients experienced significantly longer time to diagnosis and longer duration of symptoms compared to older patients[34-36]. Early-onset CRC has been associated with synchronous and metachronous CRC[37]. In early-onset CRC patients, lower awareness of CRC, lack of screening, an underappreciation of symptoms, and reluctance to seek medical care may contribute to delayed diagnosis and advanced stage at diagnosis[38].

Germline genetics

Table 2 summarizes the studies that have investigated the germline genetic and tumor molecular features of early-onset CRC. Approximately 30% of early-onset CRC patients have a family history of at least one first-degree relative with CRC[39-41]. There are a number of heritable conditions that can manifest as early-onset CRC (reviewed in detail elsewhere[39]).

Lynch syndrome, which is caused by a germline mutation in a DNA mismatch repair (MMR) gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), often manifests as early-onset CRC with high-level microsatellite instability (MSI)[42]. Studies showed that 16-35% of early-onset CRC patients had hereditary cancer-predisposing syndromes, and 34-71% of these were Lynch syndrome cases[39-41], while 45-59% of all MSI-high early-onset CRC patients had Lynch syndrome[39,41].

Familial adenomatous polyposis (FAP) is a well-known syndrome characterized by numerous colorectal adenomas in affected individuals[8]. In a typical FAP family, carriers of a germline pathogenic mutation in *APC* have a nearly 100% risk of developing CRC by age 40[8]. Increased adoption of genetic testing and prophylactic colectomy have effectively decreased CRC incidence among FAP families[43].

There exists a spectrum of cancer predisposition from single-gene Mendelian conditions to polygenic influences plus gene-by-environment (GxE) interactions. A study including over 50,000 CRCs and 58,000 controls showed that a polygenic risk score based on 95 common CRC risk variants was more strongly associated with early-onset CRC than later-onset CRC, particularly in the absence of CRC family history[30]. Compared to those with the lowest quartile, individuals with the highest quartile polygenic risk score had higher risks of early- and later-onset CRC with odds ratios of 3.7 (95% confidence interval: 3.3-4.2) and 2.9 (95% confidence interval: 2.8-3.0), respectively[30]. These findings warrant further investigation into the cumulative effect of genetic variants and interactions with environmental exposures

to clarify the etiology of early-onset CRC, and guide prevention, early detection, and treatment strategies.

Molecular pathology

CRC represents a pathologically and molecularly heterogenous group of diseases, which are influenced by exogenous and endogenous factors including the tumor immune microenvironment[44]. The continuum of molecular characteristics of CRC according to bowel subsites is compatible with the interactive roles of the microbiota and immunity in colorectal carcinogenesis[45-47]. Evidence also indicates genetic, pathological, and molecular heterogeneity in early-onset CRC[37,39-41,48-52] (Table 2).

Early-onset CRC has been associated with certain pathological features such as poor tumor differentiation and signet ring cell formation[53-55], which may reflect underlying molecular characteristics of early-onset CRC. Studies showed that signet ring cell carcinoma (defined as carcinoma with more than 50% signet ring cell component[56,57]) constituted 6.4% (65/1,016)[48] and 6.1% (26/428)[49] of early-onset CRCs in patients aged <30 years compared to 2.3% (101/4,334)[48] and 2.4% (42/1,751)[49] in those aged 30-39 years; 1.0% (49/4,774)[49] in those aged 40-49 years; and only 1.0-1.6% of later-onset CRCs[32,49,57].

Studies have shown that the prevalence of MSI-high tumors was 10-30% in early-onset CRC[37,39-41], compared to approximately 15% in overall CRC[40]. A study of mostly stage IV CRC cases (n=2,583) reported that, compared to later-onset CRC, early-onset CRC had fewer *BRAF* c.1799T>A (p.V600E) mutations, more MSI-high tumors, and fewer somatic mutations involved in the MAPK (mitogen-activated protein kinase) signaling pathway[49]. Another study using mostly advanced CRCs (n=18,218)[58] showed that, compared to later-onset CRC, early-onset CRC patients aged <40 years exhibited lower prevalence of *APC* mutation (66% vs. 80%) and *KRAS* mutation (46% vs. 52%) in non-MSI-high tumors; as for MSI-high CRC, patients under age 40 had lower *BRAF* mutation prevalence (5.2% vs. 49%) and higher prevalence of *APC* (70% vs. 34%) and *KRAS* mutations (49% vs. 24%)[58]. Other analyses revealed differences in chromosomal aberrations between early-onset and later-onset CRCs in overall CRC[52] or the non-MSI-high subset[51].

With regard to epigenetic changes, early-onset CRC has been associated positively with tumor hypomethylation of long-interspersed nucleotide elements-1 (LINE-1) and inversely with high-level CpG island methylator phenotype (CIMP)[59-61].

The distributions of consensus molecular subtypes (CMS) of CRC[62] may also differ by age of onset. The CMS system was defined by an international consortium[62] to be a classification based on comprehensive gene expression profiling. Each CMS subtype is associated with following features: CMS1, MSI-high and strong immune reaction; CMS2, activation of WNT and MYC signaling pathways; CMS3, specific metabolic signature; and CMS4, epithelial-mesenchymal transition[62]. In a study using two independent cohorts, early-onset CRC patients (n=82) and ≥70-year-old CRC patients (n=260) showed higher prevalence of CMS1 (22-23%) and lower prevalence of CMS2 (43%) and CMS4 (20-22%) compared to CRC patients aged 50-69 years (n=284) (11% CMS1, 50% CMS2, and 27% CMS4)[49]. The fraction of CMS3 was similar (12-13%) in early-onset and later-onset CRC[49].

The high CMS1 fraction in early-onset CRC patients may reflect an enrichment of Lynch syndrome MSI-high cases, supported by an even higher CMS1 fraction (44%; 11 of 25) in patients aged <40 years[49].

Treatment & prognosis

Prognostic associations of early-onset CRC (compared to later-onset CRC) are mixed (Table 3); some suggested worse[63-66] survival among early-onset CRC patients, while others reported similar[67-72] or better[32,55,73-78] prognosis. Particularly, more aggressive treatment in early-onset CRC has consistently been documented[32,55,70,72,75,78-80]. In a study using the Military Health System, early-onset CRC patients received on average 2-8 times more courses of postoperative systemic chemotherapy than later-onset CRC patients (aged 65-75 years) across all stages[72]. It remains unclear whether aggressive treatment for early-onset CRC can improve survival[55,81] or not[32,72,79]. Prognostic features, clinical management schemes, and predictive biomarkers for specific treatment regimens in early-onset CRC remain to be determined. Notably, findings across studies are often incomparable due to the heterogeneity in study designs and populations.

Why is early-onset CRC increasing?

Epidemiological factors

It should be noted that the adulthood exposures to risk factors discussed in the preceding part cannot fully explain the recent rise of early-onset CRC. If those had been risk factors for early-onset CRC, the rise of early-onset CRC would have started much earlier around the 1950s-1960s (along with the rise of later-onset CRC[8]), when many western countries started experiencing substantial lifestyle changes and increased exposure to many established CRC risk factors. Hypothetically, the “westernizing” lifestyle changes (starting around the 1950s) might have affected individuals in the early stages of life in the 1950s to 1980s. Those individuals were young adults around the 1980s to 2010s, generally coinciding with the observed rise of early-onset CRC incidence. The hypothesis that early-life exposures are risk factors for early-onset CRC[16,82] can explain the delayed rise in early-onset CRC incidence since the 1980s. In fact, the observed rise in early-onset CRC did not happen in the 1950s-1960s when the rise in later-onset CRC incidence started[8]. If this hypothesis is true, the reported associations of the adult exposures with early-onset CRC might possibly be due to unmeasured confounding by early-life exposures. Most previous epidemiological studies of early-onset CRC have utilized data on adulthood exposures but generally lack early-life information, which precludes evaluation of confounding by early-life exposures.

There has already been evidence for early-life exposures as risk factors for CRC[83-87] including early-onset CRC[24]. Analyses using the NIH AARP Diet and Health Study[83] and the Boyd Orr Cohort[84] suggested that childhood and adolescent diet was associated with the risk of CRC in general. Analyses using the Nurses’ Health Study II (NHS2)[24] and a prospective cohort of 230,000 Norwegian adolescents[85] showed that adolescent obesity was associated with increased incidence of early-onset CRC and colon cancer, respectively. Energy restriction during childhood and adolescent (due to the Dutch Hunger Winter) was associated with lower incidence of CRC[87]. In addition, studies of childhood radiation

exposure caused by atomic bombings in Japan[88], the Chernobyl nuclear accident[85], and childhood radiotherapies[89] provide evidence for early-life insults as risk factors of later cancers. However, studies on early-life exposures and adult cancers such as early-onset CRC remain scarce.

The importance of early-life information in early-onset CRC research should be recognized. The life course of each individual starts from conception and encompasses the prenatal period, infancy, childhood, adolescence, and adulthood. Early life is characterized by major physiological and metabolic changes[90,91]. Considering the acceleration of cell division and turnover, early life may represent periods of higher susceptibility to adverse effects from risk factors linked with hyperinsulinemia, increased growth factor levels, DNA damage, inefficient DNA repair, and altered microbiome. Conceivably, changes in physiology during growth in early life may cause time-varying cellular vulnerability to insults (risk factors).

Considering the possibly decades-long latency in the transition from normal cells to malignant neoplasm[92,93] and the salient birth cohort effect observed with early-onset CRC incidence, it would be prudent to evaluate early-life exposures in relation to future risk of early-onset CRC. Around the 1950s, a global shift started in diet toward higher consumption of processed meat, fast foods, edible oils, refined grains, high-fructose corn syrup, and sugar[94,95]. The global prevalence of childhood and adolescent obesity has increased more than five-fold in recent decades[96], along with reductions in physical activity[94]. Exposure to substances such as antibiotics was increasingly more prevalent in the past several decades[97,98]. Prenatal and perinatal practices have also changed with increased use of reproductive technologies, cesarean sections, and bottle feeding, which might have unforeseen long-term effects on offspring[99-101]. In adolescents, the incidence of inflammatory bowel disease (IBD), an established CRC risk factor, has increased dramatically (average annual percent changes in incidence: Crohn’s disease, 4.3% during 1988-2011; ulcerative colitis, 2.7% during 1988-1999 and 11% during 2000-2011)[102,103]. The incidence of type 2 diabetes mellitus has sharply increased by 7.1% annually during 2002-2012 in youths aged 10-19 years[104].

There exists a continuum of cancer predisposition from high-penetrance genetic conditions to moderately-penetrant variants plus/minus interactive influences of environment and low-penetrant variants to low-penetrant polygenic conditions with larger contributions of gene-by-environment (GxE) interactions. Near 100% penetrance risk variants for hereditary CRC, which certainly cause early-onset CRC, unlikely fully explain its recent rise. In contrast, low to moderately-penetrant variants with GxE interactions (especially in early-life) might contribute to the increase of early-onset CRC.

In addition, considering the apparent health disparities related to early-onset CRC[26-28], future studies should investigate how race/ethnicity, other sociodemographic factors, and their interplay relate to early-life exposures and the etiology of early-onset CRC.

Characterizing the generational shifts in early-life exposures may provide insights into the etiologies of early-onset CRC as well as childhood and other early-onset cancers. Figure 1 depicts several points for better understanding of the etiology of early-onset CRC.

Tumor molecular features

Accumulating evidence indicates that exposure to diet, chemicals, and environmental factors may cause cellular epigenetic and genetic alterations[105], leading to certain tumor molecular subtypes[106]. Compared to unexposed children and adolescents, those who had experienced famine during the “Dutch Hunger Winter” experienced lower incidence of CIMP-positive CRC but not CIMP-negative CRC[86]. Epigenetic and genetic alterations caused by certain early-life exposures might potentially contribute to the increase in early-onset CRC incidence.

LINE-1 hypomethylation, a surrogate marker of genome-wide DNA hypomethylation status, is occasionally observed in CRC[59,60,107]. A variety of exposures including ionizing radiation[108], high BMI[109], physical inactivity[109], cigarette smoking[110], pesticides[110], benzene[110], etc. have been associated with lower LINE-1 methylation levels in blood cells. Considering the association between younger age at CRC diagnosis and tumor LINE-1 hypomethylation[59,61], these exposures (together with gene-by-environment interactions), especially in early life, may play an etiological role in early-onset CRC.

A recent experimental analysis using paired normal and early-onset CRC organoid models has demonstrated its potential to reveal novel signaling pathways important in pathogenesis of early-onset CRC[111].

Microbiome & immunity

Ample evidence indicates that the gut microbiota may contribute to colorectal tumor evolution[112-114], and several species such as *Fusobacterium nucleatum*[115,116], *Escherichia coli* carrying the polyketide synthase (*pks*) island[117], and enterotoxigenic *Bacteroides fragilis*[118] as well as overall dysbiosis have been implicated[112-114]. The composition of microorganisms changes according to the anatomical location in the colorectum[119], which may relate to the epidemiological, microbial, and tumor molecular differences in CRC according to detailed colorectal subsites[8,46,47,120]. Although *F. nucleatum* may contribute to CRC development via its effects on cell proliferation and anti-tumor immunity[121], the link between *F. nucleatum* and early-onset CRC remains underexplored. In addition, *Bifidobacterium* in CRC tissue has been associated with signet ring cell formation[122], a feature that has been associated with early-onset CRC[48,49].

Prenatal, perinatal, and neonatal exposures such as maternal diabetes[123], alcohol[20], smoking[123], cesarean delivery[124], bottle feeding[124], and antibiotics use[125-127] may influence the developing microbiota and immune system. Accumulating evidence indicates that diverse immune cell types develop and mature at different gestational stages, and that these processes are essential in establishing immune tolerance and response according to developmental needs[128]. With regard to increased antibiotic use which may result in systemic and intestinal dysbiosis throughout the life course, studies have shown an association of long-term antibiotic use with CRC and colorectal adenoma[129-131]. Any ingested substances including foods, antibiotics, and chemicals (such as colorants and preservatives in modern food products[132]) may possibly alter intestinal microbes and their metabolisms and/or could be metabolized by the microbes, which can then affect fetal

physiology via umbilical circulation and amniotic fluids[133]. The long-term impact of these ingestants and altered microbial features in pregnancy and early life needs to be studied.

It is challenging to decipher the complex interactions among exposures (diet, antibiotics, chemicals, smoking, alcohol, etc.), microbiome, and host, all of which may play a significant role in CRC etiology. To examine these interactions in early life, we need prospective (and ideally longitudinal) collections of early-life information and biospecimens such as stool from pregnant mothers and children.

Primary & secondary prevention

The impact of early-onset CRC prevention in young individuals, if successful, will be substantial, considering the additional decades of life expectancy that would result. As the avoidance of risk factors is always a major primary prevention measure, further research to establish the risk factors of early-onset CRC is needed. In addition, it is recommended that early-onset CRC patients with high-level MSI or MMR protein loss undergo germline MMR gene sequencing to identify Lynch syndrome cases for prevention of future CRC in family members[42].

Although screening with stool-based tests and colonoscopy may be useful for secondary prevention of early-onset CRC, methods of screening as well as the recommended age to start screening in average-risk or higher-risk persons have yet to be widely agreed upon[134,135]. A recent systematic review on the prevalence of adenoma in colonoscopy populations, based on 19 studies comprising 19,295 individuals, reported the summary prevalence of early-onset adenoma of 11% (95% confidence interval, 8.5%−14%)[136]. The U.S. Multi-Society Task Force recommends that persons with a family history of CRC in a first-degree relative diagnosed before 60 years of age undergo colonoscopy every 5 years beginning at age 40 or 10 years before the age the relative was diagnosed, whichever is earlier[137]. In 2018, the American Cancer Society (ACS) recommended that screening start at age 45 years for average-risk persons[138]. In a nationally representative sample of individuals aged 45-49 years, past-year CRC screening rates increased from 4.8% to 12% within 2018, coinciding with the ACS guideline release[139]. The 2018 ACS recommendation to begin screening at age 45 years is based on disease burden, results from microsimulation modeling, and the reasonable expectation that screening will perform similarly in adults aged 45 to 49 years as older population[138]. Similar to prior modeling work to support the U.S. Preventive Service Task Force guidelines[140], the microsimulation modeling studies used to support the ACS guideline captured 1) observed/projected changes in cancer incidence; 2) benefits/harms of each screening modality; and 3) balance between benefits and the burden of screening. Specifically, the modeling suggests that screening every 10 years from ages 45 to 75 years achieved a ratio of incremental burden (number of colonoscopies) to benefit (life-years gained) of 32. This strategy was selected because it was on the efficient frontier and had the highest number of life-years gained among the strategies with ratios of less than 45[141].

Although screening should ideally be tailored for each person according to one’s own risk, individualized risk assessment has not yet been adopted to CRC screening

recommendations. It is likely that the assessment of genetic germline polymorphisms, early-life exposures, and their GxE interactions will improve the efficiency of screening and early-detection of early-onset CRC. However, evidence is scarce and additional studies are needed.

Transdisciplinary epidemiology

Integration of molecular biologic methods into epidemiology has become increasingly common under the umbrella term of molecular epidemiology since the 1980s[106]. More recently, the field of molecular pathological epidemiology (MPE) has substantially grown along with the increasing availability of tumor tissue resources and molecular assays in population-based studies[106,142]. The strengths of MPE research have been most apparent when an association between an exposure and a disease entity has not been established with certainty. Using the MPE approach, a putative risk factor can be linked to molecular pathology, which can provide insight into etiological mechanisms[106,142]. Moreover, when such an etiological link exists, we can expect to observe a stronger association with the specific disease subtype than with the overall disease entity that contains pathogenetically heterogeneous subtypes[106,142]. Therefore, MPE research can contribute to the establishment of causality[106,142]. Recently, the concept of MPE has been increasingly recognized in the literature[143-152]. While somewhat overlapping with the concepts of “molecular epidemiology” and “systems epidemiology”, MPE places particular emphasis on tumor tissue analyses for better pathobiological understanding.

MPE can play an important role in early-onset CRC research due to its ability to unmask previously unknown risk factors and establish causality. If a putative risk factor can be linked to specific pathogenic signatures, the MPE approach can support it as a new risk factor for early-onset CRC. Through the discovery of hidden risk factors, MPE research can inform the development of primary prevention strategies for early-onset CRC.

Challenges & opportunities

Epidemiological studies of adulthood exposures and early-onset CRC have thus far not successfully identified the root causes of its recent rise. As already discussed, if adulthood exposures were indeed risk factors for early-onset CRC, we would have observed the rise of early-onset CRC incidence even in the 1950s similar to the rise in later-onset CRC incidence. One of the major challenges in existing studies of early-onset CRC is the severe paucity of reliable early-life data. Notably, much early-life information needs to be obtained from early-life biospecimens or parents (especially mothers).

To expedite research on early-onset cancers and examine early-life risk factors, existing large-scale prospective cohort studies can be utilized. The Growing Up Today Study (GUTS)[153] has been following 16,882 children (9 to 14 years old at the time of enrollment in 1996) of female participants in the Nurses’ Health Study II (NHS2). The GUTS2 started to follow an additional cohort of 10,923 children (10 to 17 years old at the time of enrollment in 2004) of the NHS2 participants. The NHS2[24], the parent cohort of these child cohorts, has been following 116,430 participating women who were 25 to 42 years old at the

time of the study initiation in 1989. The NHS2 has prospectively collected data on exposures and various outcomes, including reproductive health and chronic diseases such as cancer. Cohorts of parent-offspring pairs can provide information in the prenatal, perinatal, neonatal, and childhood periods, which may contribute novel evidence to the study of the role of various early-life exposures in diseases during the life course. The NHS3 (https://www.nhs3.org/), which includes 45,000 U.S. nurses and nursing students aged 18 and above, recently started another recruitment phase to reach a target population of 100,000.

The Colon Cancer Family Registry (CCFR) Cohort[154], which includes 42,489 participants from 15,049 families, was established in 1997 as an international consortium of six centers in North America and Australia. The CCFR collected information regarding family history of cancer and CRC risk factors, as well as biospecimens (blood and paraffin-embedded tumor tissue). During phase II recruitment (2002-2007), the population-based recruitment efforts targeted early-onset CRC cases. They have identified over 3,000 early-onset CRC cases[154]. In the future, this study will contribute to the clarification of the genetic and environmental etiologies of early-onset CRC.

The Child Health and Development Studies (CHDS)[155], which includes over 15,000 women and their 19,000 children, was initiated in 1959 to investigate the associations of biological, genetic, and early-life factors with health outcomes in adults. The biospecimens and data on early-life to adult exposures collected over the past 60 years will provide us with a unique resource to evaluate the relationship between early-life exposures and long-term health outcomes.

The National Children's Study (https://www.nichd.nih.gov/research/supported/NCS) was an ambitious project with goals to recruit and follow 100,000 children in the U.S. from prenatal to adulthood periods, and to study environmental influences on child health and development. Although the study was closed in 2014, a reactivation of the study or following-up of the former participants has been suggested[156], which may provide invaluable opportunities to study the etiologies of childhood and early-onset cancers.

Growing Up in New Zealand[157] is a longitudinal study that includes more than 6,000 children and their families. This study was designed to recruit and follow a cohort of children from the prenatal period onward. Findings from this study may provide yet more evidence on early-life exposures and early-onset cancers.

There are several other studies that have the potential to provide new insight into early-onset CRC[156]; those include the UK Millennium Cohort Study[158] and the ORIGINS Project (https://originsproject.telethonkids.org.au/) in Australia. These studies will provide opportunities to clarify the effect of early-life exposures on long-term health outcomes including cancer.

Importantly, these valuable datasets and any other relevant studies may be harmonized, combined, and/or integrated to increase the validity of findings and illuminate further information on the etiologies of a multitude of health conditions throughout the life course, including (but not limited to) early-onset CRC.

Conclusion & future direction

Although the causes of the rise of early-onset CRC remain uncertain, we can deploy and implement several measures relatively fast. Those include (1) education of physicians, other healthcare workers, and general individuals; (2) re-evaluation of screening guidelines for early-onset CRC; (3) etiological research for identifying genetic and epidemiologic risk factors; and (4) better coordination of clinical care and communication for early-onset CRC patients[82]. We advocate the roadmap of the general strategies in Table 4. Education of healthcare providers, patients, and general individuals regarding the rise of early-onset CRC may lead to prevention and early detection. It would be ideal that researchers learn the importance of longitudinal life-course cohort studies combined with prospective biospecimen collections.

Thus far, attempts to identify adulthood exposures as risk factors for early-onset CRC have seen only limited success. Clues may emerge when we carefully consider (1) the likely long (years to decades) growth / incubation time of colorectal neoplasms; (2) the environmental, dietary, and lifestyle changes that have occurred over the past century; (3) the observed birth cohort effects; (4) the drastic biophysiological changes that occur in each individual from conception to adulthood; and (5) the differential clinical, pathological, and molecular features of early-onset CRC compared to later-onset CRC. It is conceivable that currently unknown etiological factors, possibly those that begin in early life (from the prenatal to adolescent periods), may be driving the rise of early-onset CRC incidence. Challenges include the paucity of large-scale longitudinal studies that can provide accurate information on long-term exposures from early life to adulthood. We must develop life-course epidemiological studies, which should be combined with prospective biospecimen collections (stool, blood, saliva, urine, placenta, amniotic fluid, cord blood, etc.), state-of-the-art omics (including genomic, metagenomic, and metabolomic research), and analyses of molecular pathology, immunity, and the tumor microenvironment[159]. Importantly, such prospective cohorts, once established, can be utilized to elucidate the etiologies of not only early-onset CRC but also many other diseases including childhood cancers and other early-onset malignancies. We can consider a following scenario: if we have resources, should we invest to establish (A) 10 parent-offspring paired prospective cohorts vs. (B) 100 case-control studies? In the former, we can study not only early-life exposures but also dozens of diseases of children and adults. In the latter, each study can assess only one disease of interest, and cannot fully evaluate early-life exposures from adult subjects, such as early-onset CRC patients. It is quite evident which can benefit us more in the long run. Hence, prudent investment of our finite resources, funds, and efforts into building longitudinal prospective cohort infrastructure including biobanks should be our key priority.

In the meantime, astute use of existing datasets and resources including large prospective cohort studies to examine early-life information offers a relatively cost- and time-efficient means to expedite etiological research on early-onset CRC and other early-onset cancers.

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Abbreviations:

ACS	American Cancer Society
AJCC	American Joint Committee on Cancer
BMI	body mass index
CCFR	Colon Cancer Family Registry
CHDS	Child Health and Development Studies
CIMP	CpG island methylator phenotype
CMS	consensus molecular subtype
CRC	colorectal cancer
FAP	familial adenomatous polyposis
GxE	gene-by-environment
GUTS	Growing Up Today Study
IBD	inflammatory bowel disease
LINE-1	long interspersed nucleotide element-1
MMR	mismatch repair
MPE	molecular pathological epidemiology
MSI	microsatellite instability
NHS2	Nurses' Health Study II
NHS3	Nurses' Health Study 3
pks	polyketide synthase

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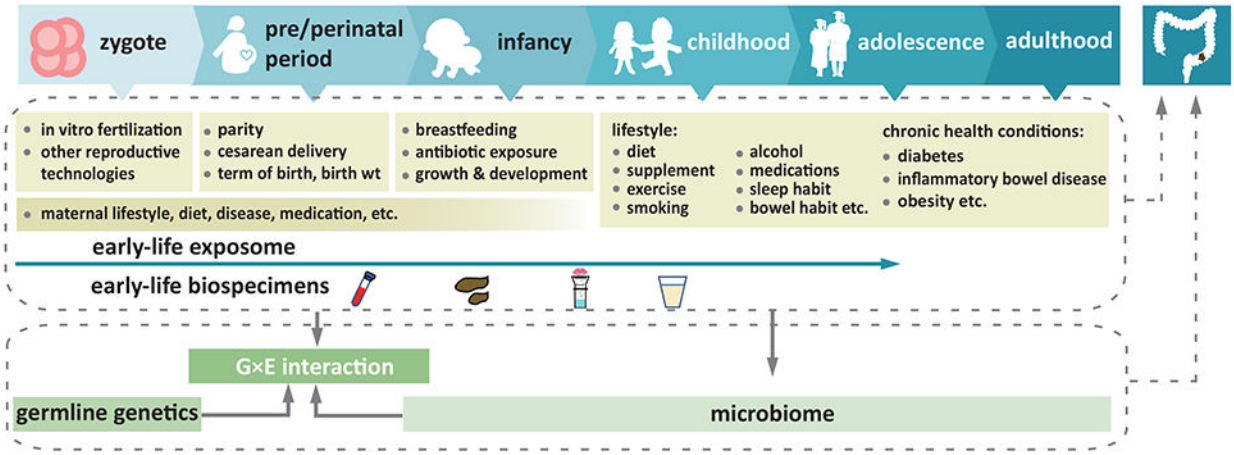

Figure 1.

Illustration of potential effects of various life-course exposures on tumor development from early life (the prenatal to adolescent periods) to adulthood. The exposome indicates the totality of exposures and interactions thereof. The gene-by-environment (GxE) interactions during life-course may play an important role in the etiology of early-onset colorectal cancer. Early-life biospecimens such as stool, blood, saliva, urine, cord blood, placenta, etc., which can be collected from either mother or fetus/neonate or both, may be able to provide early-life information when analyzed in the future.

Abbreviations: GxE, gene-by-environment; wt, weight.

Table 1.

Epidemiological studies of early-onset colorectal cancer and early-onset adenoma.

Ref No.	Authors (year)	Country	Study design	Study population, No.	Case, No. (diagnosed age)	Risk factors, OR/HR (95% CI)*
20	Rosato *et al.* (2013)	Italia and Switzer-land	Case-control study	329 EOCRC and 1,361 age-matched controls	EOCRC, 329 (≤45)	Family history of CRC in first-degree relatives (yes vs no), 4.5 (2.6–7.7); alcohol (≥14 drinks/week vs never drinking), 1.6 (1.1–2.2); processed meat (highest vs lowest tertile), 1.6 (1.1-2.2); vegetables (highest vs lowest tertile), 0.40 (0.28-0.56); citrus fruit (highest vs lowest tertile), 0.61 (0.45-0.84); fish (highest vs lowest tertile), 0.78 (0.60-1.00); β-carotene (highest vs lowest tertile), 0.52 (0.37-0.72); vitamin C (highest vs lowest tertile), 0.68 (0.49-0.94); vitamin E (highest vs lowest tertile), 0.38 (0.26-0.58); folate (highest vs lowest tertile), 0.59 (0.40-0.86).
123	Kim *et al.* (2016)	Korea	Cross-sectional study	564 advanced adenoma and CRC and 59,782 controls Kangbuk Samsung Health Study	Advanced adenoma and EOCRC, 564 (<50)	Age (per year), 1.08 (1.07-1.10); male (vs female), 1.3 (1.0-1.6); smoking (current vs never/ former): 1.4 (1.2-1.6); CRC family history (yes vs no), 1.5 (1.0-2.1); diabetes mellitus-related factors (yes vs no), 1.3 (1.1-1.5); obesity (yes vs no), 1.2 (1.0-1.5); low-density lipoprotein-cholesterol (per mg/dL), 1.01 (1.01-1.02); carcinoembryonic antigen (per ng/mL), 1.04 (1.01-1.09).
23	Nguyen *et al.* (2018)	United States	Prospective cohort study	89,278 females The Nurses' Health Study II	EOCRC, 118	Sedentary TV viewing time (>14 vs ≤7 hours per week), 1.69 (1.07-2.67).
21	Gausman *et al.* (2019)	United States	Case-control study	269 EOCRC, 2,802 LOCRC, and 1,122 controls (age-matched, cancer-free individuals)	EOCRC, 269; LOCRC, 2802	EOCRC vs LOCRC: male (vs female), 1.4 (1.1-1.9); non-Hispanic black (vs non-Hispanic white), 1.7 (1.1-2.7); non-Hispanic Asian (vs non-Hispanic white), 2.6 (1.6-4.2); IBD (yes vs no), 3.0 (1.2-6.6); family history of CRC (yes vs no), 2.9 (1.9-4.3). EOCRC vs controls: male (vs female), 1.9 (1.4-2.5); family history of CRC (yes vs no), 8.6 (4.8-15).
160	Kim *et al.* (2019)	Korea	Cross-sectional study	622 advanced adenoma and CRC and 71,734 controls Kangbuk Samsung Health Study	Advanced adenoma and EOCRC, 622 (20-39)	Diagnosed 20-29 years old: obesity (BMI ≥25 vs <25 kg/m^2), 2.5 (1.2-4.9); waist circumference (>90 cm in men or >80 cm in women vs ≤90 cm in men or ≤80 cm in women), 2.3 (1.1-4.5); elevated triglyceride level (≥150 vs <150 mg/dL), 3.0 (1.4-6.2). Diagnosed 30-39 years old: age (per year), 1.09 (1.06-1.13); smoking (current/former vs never), 1.3 (1.1-1.6); alcohol intake (≥20 vs <20 g/day), 1.3 (1.1-1.6); BMI (≥25 vs <25 kg/ m^2), 1.3 (1.1-1.6); waist circumference (>90 cm in men or >80 cm in women vs ≤90 cm in men or ≤80 cm in women), 1.3 (1.1-1.6).
24	Liu *et al.* (2019)	United States	Prospective cohort study	85,256 females the Nurses' Health Study II	EOCRC, 114	Obese (BMI ≥30 vs 19-23 kg/m^2), 2.0 (1.2-3.3); BMI (≥23 vs 18.5-21 kg/m^2) at 18 years of age, 1.6 (1.0-2.6); weight gain since 18 years of age (≥40 kg vs loss or gain <5 kg), 2.2 (1.0-4.6).
22	Low *et al.* (2020)	United States	Case-control study	651 EOCRC and 67,416 controls	EOCRC, 651	Age (per year), 1.05 (1.03-1.07); male (vs female), 2.2 (1.7-2.9); aspirin use (yes vs no), 0.7 (0.5-0.8); overweight (vs normal weight), 0.69 (0.55-0.87); obese (vs normal weight), 0.69 (0.55-0.86); weight loss ≥5 kg within 5-year period preceding colonoscopy (yes vs no), 2.2 (1.8-2.8).

Studies with 200 or fewer cases may not be listed except for studies examining key features.

*Statistically significant using two-sided p <0.05.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; HR, hazard ratio; IBD, inflammatory bowel disease; LOCRC, later-onset colorectal cancer; OR, odds ratio.

Table 2.

Previous studies of germline genetic and somatic molecular characteristics of early-onset colorectal cancer.

Ref No.	Authors (year)	Country	No. of cases (diagnosed age)	MSI-high	Pathogenic germline mutation	Lynch syndrome*	Notes
37	Liang *et al.* (2003)	China	138 CRC (<40) vs 339 (≥60)	37/126 (30%)	NA	NA	High-frequency MSI (30% vs 6.3%; p <0.001), and synchronous CRC (6% vs 1%; p = 0.007) were observed in EOCRC compared to LOCRC.
61	Baba *et al.* (2010)	United States	196 CRC (<60) vs 673 (≥60)	NA	NA	NA	LINE-1 hypomethylation** were more prevalent in patients aged <60 years than patients aged ≥60 years (p = 0.006). [***Frequencies of LINE-1 methylation level <50% in EOCRC (n = 27) and LOCRC (n = 842) were 22% and 11%, respectively (p = 0.08).]
51	Berg *et al.* (2010)	Norway	23 EOCRC vs 17 LOCRC in non-MSI-high	NA	NA	NA	Ten genomic loci listed below were identified as more often altered in tumors from early-onset versus late-onset CRC; gains of 2q35, 10q21.3-22.1, 10q22.3 and 19q13.2-13.31 and losses from 1p31.3, 1q21.1, 2q21.2, 4p16.1-q28.3, 10p11.1 and 19p12.
59	Antelo *et al.* (2012)	Argentina	185 EOCRC vs 135 LOCRC	NA	NA	NA	EOCRC showed lower mean LINE-1 methylation level (57%) than LOCRC [MSI-high set (n = 46; 67%), non-MSI-high set (n = 89; 65%), both p < 0.0001].
50	Perea *et al.* (2014)	Spain	82 EOCRC vs 97 LOCRC	12 (15%)	NA	10 (12%)	Early-onset non-MSI-high CRCs showed different tumor locations (p = 0.02) and more family history of cancer (p <0.001) compared to late-onset non-MSI-high CRCs.
41	Mork *et al.* (2015)	United States	193 EOCRC (≤35)	45 (23%)	67 (35%)	23 (12%)	Identifiable hereditary cancer syndromes other than Lynch syndrome were as follows; familial adenomatous polyposis (16 patients), constitutional mismatch repair deficiency (2 patients), biallelic *MUTYH* mutations (2 patients), and Li-Fraumeni syndrome (1 patient).
52	Arriba *et al.* (2016)	Spain	60 EOCRC vs 86 LOCRC	NA	NA	NA	Losses at 1p36, 1p12, 1q21, 9p13, 14q11, 16p13, and 16p12 were significantly more frequent in early-onset CRC, whereas gains at 7q11 and 7q22 were more frequent in later-onset CRC.
40	Pearlman *et al.* (2017)	United States	450 EOCRC	48 (11%)	72 (16%)	37 (8.2%)	Germline mutations associated hereditary cancer syndrome except Lynch syndrome were found in the following genes; *APC* (9 patients), *ATM* (4 patients), *BRCA1* (2 patients), *BRCA2* (4 patients), *CDKN2A* (1 patient), *CHECK2* (1 patient), *MUTYH* (9 patients), *PALB2* (2 patients), and *SMAD4* (1 patient).
39	Stoffel *et al.* (2018)	United States	315 EOCRC	41 (9.5%)	79 (25%)	56 (18%)	Germline mutations associated hereditary cancer syndrome except Lynch syndrome were found in the following genes; *APC* (10 patients), in *BRCA1* (1 patient), *CHEK2* (1 patient), *MUTYH* (8 patients), *SMAD4* (2 patients), and *TP53* (1 patient).
58	Lieu *et al.* (2019)	United States	1,420 EOCRC (<40), 3,248 EOCRC (40-49) vs 13,550 LOCRC	NA	NA	NA	*TP53* (FDR < 0.01) and *CTNNB1* (FDR = 0.01) mutations were more prevalent in EOCRC patient aged <40 years. In the MSI-high cohort, *APC* (p <0.001, FDR <0.01) and *KRAS* (p < 0.001, FDR < 0.01) mutations were more prevalent in EOCRC patients aged <40 years, compared to LOCRC patients aged ≥50 years.
49	Willauer *et al.* (2019)	United States	1,162 EOCRC vs 2,583 LOCRC (2 cohorts; mostly stage IV)	68 (4.5%) in one stage IV cohort of	NA	NA	EOCRC had fewer *BRAF* c.1799T>A (p.V600E) mutations (4.8%) and higher MSI-high (7.4%) compared to LOCRC (8.1%, p < 0.0001; and 3.0%, p = 0.04, respectively).

Ref No.	Authors (year)	Country	No. of cases (diagnosed age)	MSI-high	Pathogenic germline mutation	Lynch syndrome*	Notes
				1525 CRCs			
49	Willauer *et al.* (2019)	United States	82 EOCRC vs 544 LOCRC	Same as above	NA	NA	EOCRC patients and ≥70-year-old LOCRC patients (n = 260) had similar CMS distributions, showing higher CMS1 (22-23%) and lower CMS2 (43%) and CMS4 (20-22%) compared to LOCRC patients aged 50-69 years (n = 284) (11% CMS1, 50% CMS2, and 27% CMS4).
30	Archambault *et al.* (2020)	United States	5,479 EOCRC vs. 44,544 LOCRC	NA	NA	37 (6.4%, among 574 cases)	Polygenic risk score developed from 95 CRC-associated common genetic risk variants identified by GWAS were significantly associated with EOCRC.

Studies with 100 or fewer cases having tumor tissue data may not be listed, except for studies examining key features.

*Lynch syndrome was defined by the presence of a germline pathogenic mutation in any of MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).

**LINE-1 methylation level (described as 0 to 100) was calculated by the average of methylated cytosine after bisulfite conversion among at the four CpG sites. LINE-1 hypomethylation was defined as < 40%.

***Unpublished data.

Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; FDR, false discovery rate; GWAS, genome-wide association studies; LINE-1, long-interspersed nucleotide element-1; LOCRC, later-onset colorectal cancer; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; MSI, microsatellite instability; NA, not available.

Table 3.

Previous studies of prognosis and treatment of early-onset colorectal cancer.

Ref No.	Authors (year)	Country	No. of cases (diagnosed age)	Prognosis / treatment
77	O'Connell *et al.* (2004)	United States	1,334 EOCRC (20-40) vs 46,457 LOCRC (60-80)	The 5- year CRC-related survival of young CRC vs older CRC patients was 93% vs 95% (*p*, NS) for stage I, 89% vs 83% ($p = 0.01$) for stage II, and 59% vs 57% (*p*, NS) for stage III: 18% vs 6% ($p < 0.001$) for stage IV.
75	Quah *et al.* (2007)	United States	68 EOCRC (≤40) vs 1,259 older CRC (>40) in Stage I-III	The 5-year CRC-related survival of young vs older CRC patients was 86% vs 87% (*p*, NS). The 5-year OS was higher in the EOCRC (84% vs 73%, $p = 0.001$). Young patients were also more likely to receive adjuvant chemotherapy, especially in the stage II: 39% vs 14%, ($p = 0.003$).
71	McMillan *et al.* (2009)	United Kingdom	99 EOCRC (<45) vs 1,978 older CRC (≥45)	Compared with young CRC patients aged <45, older CRC patients aged ≥45 had no significant difference in their hazard ratios for cancer-specific survival.
64	Sultan *et al.* (2010)	Jordan	159 EOCRC (4-20) in 550,622 CRC	SEER: The 5-year relative survival of young CRC vs older CRC were 40% vs 60% ($p < 0.001$). The 10-year relative survival, 31% vs 54%.
67	Blanke *et al.* (2011)	Multiple countries *	793 EOCRC vs 5,491 LOCRC in stage IV	Results from phase III trials. Response rate and OS were similar in CRC patients aged <50 and ≥50 in stage IV; PFS was minimally worse in the younger cohort (6.0 v 7.5 months; $p = 0.02$).
78	Hubbard *et al.* (2012)	United States	5,817 EOCRC vs 27,757 LOCRC	Younger patients aged <40 or <50 years with stage II and III colon cancer had longer OS and DFS than older patients. Younger patients (aged <40 or <50) with stage II and III colon cancer derive similar benefit from adjuvant therapy as older patients.
73	Schellerer *et al.* (2012)	Germany	244 EOCRC vs 1,718 LOCRC	The 5- year CRC-related survival of EOCRC vs LOCRC patients was 89% vs 80% ($p = 0.01$) for M0 rectal cancer, 21% vs 12% ($p = 0.06$) for M0 rectal cancer, 84% vs 89% (*p*, NS) for M1 colon cancer, 13% vs 15% (*p*, NS) for M1 colon cancer.
70	Yang *et al.* (2012)	China	530 EOCRC (≤44) vs. 2,626 CRC (>44)	Compared to older patients, young patients received chemotherapy and died of cancer related causes. OS, DFS and cancer-specific survival of younger patients were comparable to older patients.
63	Lieu *et al.* (2014)	United States	3,051 EOCRC in 20,023 stage IV CRC	Relative to patients of middle age CRC, young CRC patients had 19% (95% CI, 7-33%) increased risk of death and 22% (95% CI, 10-35%) increased risk of progression. The age effect did not differ by sites of metastatic disease, year of enrollment, types of therapy received, or biomarker mutational status.
32	Kneuertz *et al.* (2015)	United States	13,102 EOCRC (18-49) vs 37,007 LOCRC (65-75)	The 5-year CRC-related survival of young vs older CRC patients was 91% vs 90% for stage II overall, 95% vs 95% for stage II low risk, and 88% vs 86% for stage II high risk. Almost 6% of the patients with young-onset stage I received adjuvant chemotherapy. Adjuvant chemotherapy was administered for 51% of young patients and 9% of older patients.
81	Orsini *et al.* (2015)	Netherlands	1,102 EOCRC (≤40) vs 35,954 CRC (41-70)	Young age was a prognostic factor for better survival in stage I-III patients. Adjuvant chemotherapy was more often given to young CRC patients (24% vs 14%, $p < 0.001$). Adjuvant chemotherapy in young stage III and pN1 patients was associated with improved survival.
74	Wang *et al.* (2015)	Sweden and United States	43,821 EOCRC vs 466,113 LOCRC	SEER: The 5-year relative survival of young CRC vs older CRC were 67% vs 61% ($p < 0.001$) in SEER database; 75% vs 63% ($p = 0.25$) in Linköping Cancer database.
80	Abdelsattar *et al.* (2016)	United States	37,847 EOCRC vs 220,177 LOCRC (50-75)	SEER: CRC patients with distant metastasis were more likely to receive surgical therapy for their primary tumors in younger age group (adjusted probability: 72% vs 63%; $p < 0.001$), and radiation therapy was more likely in younger CRC patients (adjusted probability: 53% vs 48%; $p < 0.001$).
76	Boyce *et al.* (2016)	Australia	2,001 EOCRC vs 30,177 LOCRC	5-year cancer-specific survival was greater for patients with EOCRC than for LOCRC (69% vs 66%) ($p < 0.001$).

Ref No.	Authors (year)	Country	No. of cases (diagnosed age)	Prognosis / treatment
29	Holowatyj *et al.* (2016)	United States	28,145 EOCRC	SEER: The 5-year OS was 55% among non-Hispanic blacks, 68% among non-Hispanic whites, and 63% among Hispanic individuals (p <0.001).
65	Kim *et al.* (2016)	Korea	693 EOCRC (≤45) vs 1,823 LOCRC (56-65)	The 5-year cancer-specific survival rate was 81% in the young group and 88% in the older group (p <0.001). No significant difference in OS for each stage.
66	Chou *et al.* (2017)	Taiwan	3,395 EOCRC (≤40) in 61,789 CRC	Young CRC (≤40) had poorer OS and cancer-specific survival compared to older CRC (41–50 and 51–60) groups, although this trend was reversed in the 71–80 and >80 age groups.
72	Manjelievskaia *et al.* (2017)	United States	671 EOCRC, 1,599 LOCRC (50-64), and 873 LOCRC (≥65)	EOCRC and middle-aged CRC patients were more likely to receive multiagent chemotherapy than older patients (EOCRC: OR, 2.5; 95% CI, 1.4-4.3 and middle-aged CRC: OR, 2.7; 95% CI, 1.7-4.2). Among patients who received surgery and postoperative systemic chemotherapy, no significant differences were observed in survival among age groups.
68	Pokharkar *et al.* (2017)	India	351 EOCRC (≤45) vs 427 CRC (>45)	No statistically significant difference was found in OS between young and old CRC patients.
69	Rho *et al.* (2017)	Multiple countries**	224 EOCRC (≤44) vs 274 CRC (>44)	The mortality analysis showed no significant differences between the two groups. The longitudinal treatment patterns for both groups were similar but more biological therapy was used for young CRC.
79	Kolarich *et al.* (2018)	United States	9,126 EOCRC vs 33,980 LOCRC (50-75)	The receiving rates of radiation therapy were 42 % in stage I EOCRC patients and 32% in LOCRC patients, respectively (p < 0.001); the receiving rates of chemoradiation therapy were 94% in stage II and III EOCRC patients and 88% in stage II and III LOCRC patients.
55	Rodriguez *et al.* (2018)	Canada	107 EOCRC (≤40) vs. 5,364 LOCRC (>60)	Compared with patients aged > 60 years, adjuvant chemotherapy was delivered more often to younger CRC patients aged ≤40 years for stage II (50% vs 13%; p <0.001) and stage III (> 92% vs 57%; p <0.001), respectively. OS and cancer-specific survival were superior for the patients aged ≤40 years compared with the patients aged >60 years.

Studies with 100 or fewer cases or cases overlapping with another study (eg, SEER database) may not be listed, except for some studies.

*France, Germany, United Kingdom, and United States.

**Bulgaria, Canada, Czech Republic, Georgia, Ireland, and Italy.

Abbreviations: CI, confidence interval; CRC, colorectal cancer; DFS, disease-free survival; EOCRC, early-onset colorectal cancer; LOCRC, later-onset colorectal cancer; NS, not significant; OR, odds ratio; OS, overall survival; PFS, progression-free survival; SEER, Surveillance, Epidemiology, and End Results.

Table 4.

Roadmap of strategies to reduce the public health burden of early-onset CRC.

Theme	Strategy	Note
1: Education	1.1: Educate physicians, other healthcare workers, and general individuals to raise awareness of early-onset CRC.	This can be implemented.
2: Screening	2.1: Expand genetic testing for individuals with family history of CRC. 2.2: Conduct research to create and refine prediction models for early-onset CRC. 2.3: Evaluate available evidence and screening guidelines for early-onset CRC. 2.4: Develop personalized screening strategies.	Further research, including comparative effectiveness research, is needed.
3: Etiological research	3.1: Utilize existing resources to study etiologies. 3.2: Design additional studies, including life-course cohort studies, combined with biospecimen collections and omics analyses. 3.3: Study genetic and epidemiologic risk factors, including early-life exposures, (and GxE interactions) for early-onset CRC. 3.4: Study etiological mechanisms using experimental model systems.	Determination of risk factors and their effect sizes can help us improve primary, secondary, and tertiary prevention strategies.
4: Clinical care and research	4.1: Set up specialized centers, units, and/or clinics focused on early-onset CRC, to deliver improved care. 4.2: Conduct clinical trials to determine personalized treatment strategies. 4.3: Communicate with early-onset CRC patients regarding treatment options and considerations as well as implications for potential familial risks.	Randomized clinical trials integrated with assessments of tumor characteristics (including tissue microbiota and immunity) are needed. Genetic, fertility, and social counseling may be indicated for patients.

Abbreviation: CRC, colorectal cancer; GxE, gene-by-environment.