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Decoding the genetic and environmental forces in propelling the surge of early-onset colorectal cancer

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Abstract

Early-onset colorectal cancer (EOCRC) shows a different epidemiological trend compared to later-onset colorectal cancer, with its incidence rising in most regions and countries worldwide. However, the reasons behind this trend remain unclear. The etiology of EOCRC is complex and could involve both genetic and environmental factors. Apart from Lynch syndrome and Familial Adenomatous Polyposis, sporadic EOCRC exhibits a broad spectrum of pathogenic germline mutations, genetic polymorphisms, methylation changes, and chromosomal instability. Early-life exposures and environmental risk factors, including lifestyle and dietary risk factors, have been found to be associated with EOCRC risk. Meanwhile, specific chronic diseases, such as inflammatory bowel disease, diabetes, and metabolic syndrome, have been associated with EOCRC. Interactions between genetic and environmental risk factors in EOCRC have also been explored. Here we present findings from a narrative review of epidemiological studies on the assessment of early-life exposures, of EOCRC-specific environmental factors, and their interactions with susceptible loci. We also present results from EOCRC-specific genome-wide association studies that could be used to perform Mendelian randomization analyses to ascertain potential causal links between environmental factors and EOCRC.

Keywords: Early-onset colorectal cancer; Environmental factors; Genetic factors; Interaction; Germline variants; Genome-wide association study; Lifestyle

Introduction

According to the 2022 global and regional cancer statistics, colorectal cancer accounted for 1,926,118 new cases, representing 9.6% of all cancer cases, ranking third in incidence, and 9.3% of cancer deaths, ranking second in mortality.[1] The incidence of colorectal cancer in high-income regions has stabilized, yet it remains higher than in low- and middle-income countries.[2] In contrast, in low- and middle-income countries, the incidence has been increasing. In this study, we refer to colorectal cancer patients younger than 50 years old as early-onset colorectal cancer (EOCRC).[3] Notably, EOCRC shows a different epidemiological trend compared to later-onset colorectal cancer (CRC), with its incidence rising in most regions and countries worldwide.[4] According to data from Global Burden of Disease 2021, the age-standardized incidence rate (ASIR) of EOCRC globally in 2021 was 5.37 (95% confidence interval [CI]: 5.34, 5.39) per 100,000. Notably, Netherlands, Canada, United States, Australia, Portugal, and China have high ASIRs for EOCRC in 2021, with China's high ASIR indicating the rapid rise of EOCRC in middle-income countries.

Most colorectal cancer screening guidelines worldwide recommend starting general population bowel cancer screening at the age of 50 years. However, some guidelines, such as those from the US Preventive Services Task Force, the Chinese Guidelines for Colorectal Cancer Screening and Early Diagnosis and Treatment, and the National Guidelines for Colorectal Cancer Screening in Saudi Arabia, have lowered the starting age to 40 or 45 years. This lowering of colorectal cancer screening age may lead to detecting more EOCRC cases among

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individuals aged 40–45 years, but it may also increase the burden for endoscopy investigations. However, some projections indicate that by 2030, EOCRC will account for 11% of all colon and 23% of all rectal cancer cases across different regions.[3] The reasons behind the global increase in EOCRC incidence remain largely unknown, and the underlying causes and mechanisms are not fully understood.

Aside from EOCRC being strongly associated with genetic conditions like Lynch syndrome and Familial Adenomatous Polyposis (FAP), the increase in EOCRC incidence over recent decades is primarily attributed to the rise in sporadic EOCRC cases.[3] Environmental risk factors, including obesity, smoking, alcohol consumption, dietary habits, and sedentary behavior, are recognized as significant contributors to the increase in sporadic EOCRC and early-onset advanced colorectal adenomas.[5] Some studies have found that, in contrast to late-onset colorectal cancer, EOCRC exhibits differences in molecular characteristics, including a higher proportion of specific gene mutations, microsatellite instability, and a lower level of DNA methylation, while EOCRC patients typically present with descending colonic or rectal cancer, advanced disease stage, and unfavorable histopathological features.[6] This narrative review focuses on the environmental risk factors and genetic susceptibility related to EOCRC in recent years, aiming to facilitate the identification of high-risk individuals and provide significant insights for the prevention of EOCRC from the perspective of gene–environment interactions.

Genetics of EOCRC

Germline variants associated with EOCRC

The prevalence of pathogenic germline mutations in cancer susceptibility genes is significantly higher in EOCRC compared to the overall colorectal cancer population.[7] Approximately 20% of EOCRC cases can be attributed to hereditary cancer syndromes as the underlying etiology.[3] Hereditary colorectal cancer syndromes primarily include Lynch syndrome and FAP, which are associated with an increased risk of colorectal cancer and typically manifest at an earlier age.[3] The lifetime risk of colorectal cancer for different types of Lynch syndrome pathogenic mutations ranges from 15% to 52%, whereas for classic FAP, the risk approaches nearly 100%.[8] Other hereditary colorectal cancer susceptibility syndromes encompass *MUTYH*-associated polyposis, polymerase proofreading-associated polyposis (PPAP), Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), *PTEN* hamartoma tumor syndrome (PHTS), also known as Cowden syndrome, mixed polyposis, and serrated polyposis syndrome.

In EOCRC patients, the most common germline pathogenic mutations are found in genes associated with Lynch syndrome, such as *MLH1*, *MSH2*, *EPCAM*, *MSH6*, and *PMS2*, which occur in 2–5% of patients.[9] Despite the strong familial heritability associated with EOCRC, two-thirds of EOCRC cases are sporadic, suggesting that sporadic EOCRC may represent a distinct subtype of colorectal cancer with specific molecular characteristics. Considering that the prevalence of Lynch syndrome and FAP hereditary cancer syndromes is not expected to have changed significantly, the recent increase in EOCRC may be primarily due to sporadic cases.

Patients with EOCRC exhibit a broad spectrum of pathogenic germline mutations, yet these are often not accompanied by the anticipated phenotype or family history. A study by Stoffel *et al*[7] discovered that among 315 EOCRC patients, 79 (25%) possessed a pathogenic germline mutation; 20 of these patients had variations associated with polyposis conditions, such as *APC* and *SMAD4*. Yurgelun *et al*[10] conducted a germline panel test for 25 genes on 336 EOCRC patients and identified 47 (14%) with pathogenic mutations. These included 22 related to Lynch syndrome, three *APC* mutations, three bi-allelic *MUTYH* mutations, six *BRCA1/2* mutations, and one *BRIP1* mutation. Pearlman *et al*[11] performed a similar multi-gene panel test on 450 EOCRC patients, finding 72 (16%) with a pathogenic germline mutation; 38 (8%) had a Lynch syndrome gene mutation, and 11 patients had polyposis gene mutations—six with FAP, four with bi-allelic *MUTYH*, and one with *SMAD4*. In addition, there were six unexpected *BRCA1/2*, four *ATM*, two *PALB2*, and one each of *CHEK2* and *CDKN2A* mutations. Mutations associated with Lynch syndrome and FAP are typically found in genes with high penetrance and researchers have also identified mutations in genes with moderate penetrance in patients with EOCRC. Although these mutations are common, their precise role in EOCRC remains unclear. In the study conducted by Yurgelun *et al*[10], 16 out of 106 variants (15%) were in genes of moderate penetrance. Similarly, in Pearlman *et al*[11], 15 out of 72 variants (21%) were found to be of moderate penetrance. Finally, a significant proportion of patients with pathogenic mutations neither exhibit the characteristics of associated syndromes nor have a family history.[6] For these individuals, clinical screening is of paramount importance, since accurate and early detection can significantly improve the clinical management and outcomes for patients with EOCRC.

Specific susceptibility loci for EOCRC

Zhang *et al*[5] conducted a meta-analysis including 61 studies that reported on 62 genetic variants, finding no significant associations between the examined genetic variants and EOCRC risk. Recently, Wang *et al*[12] conducted a large-scale genome-wide association study (GWAS) on sporadic EOCRC and identified 49 EOCRC-specific risk loci. The candidate gene mapping and pathway analysis highlighted 88 potential functional genes and their involvement in various pathways. The polygenic risk scores (PRS) derived from these single nucleotide polymorphisms (SNPs) significantly improved risk prediction of EOCRC in the Genetic Epidemiology of Colorectal Cancer Consortium and UK Biobank cohorts, with the top EOCRC-specific variant, rs12794623, found to regulate *POLA2* expression, impacting EOCRC oncogenesis.[12] Archambault *et al*[13] conducted a GWAS analysis involving 12,197 EOCRC patients and 95,860 late-onset colorectal cancer individuals and found that the early-onset patients were more strongly associated with a PRS developed from 95 CRC-associated common genetic risk variants. Interestingly,

patients with EOCRC without a family history exhibited an even stronger association with this PRS (odd ratio [OR] 4.26, 95% CI: 3.61–5.01). Recently, Laskar *et al*[14] conducted a GWAS analyzing 65,829 controls and 6,176 individuals with EOCRC. Their research identified two novel risk loci for EOCRC at 1p34.1 and 4p15.33, in addition to identifying multiple established risk loci. The study underscored the significance of insulin signaling and pathways related to immune and infectious processes in EOCRC, highlighting the substantial role of non-coding signals in the genetic susceptibility to EOCRC. However, the study was only able to account for 6.2% of the SNP-based heritability of EOCRC, underscoring the necessity for larger-scale GWAS and whole-genome sequencing studies. These future endeavors will be pivotal in identifying the missing heritability and in providing further biological insights into the susceptibility to EOCRC, thereby leading to personalized approaches in prevention and treatment. Results for EOCRC risk loci are presented in Supplementary Table 1, http://links.lww.com/CM9/C421.

Genetic and molecular mechanisms for EOCRC

Sporadic EOCRC patients are more likely to present with *BRAF* mutations, lack of methylation, and chromosomal instability.[15] Although most EOCRC tumors were found to be microsatellite stable and to not exhibit DNA repair defects, the proportion of microsatellite instability was found to be higher in EOCRC compared to late-onset colorectal cancer.[11] Among microsatellite stable colorectal cancer, diploidy was found to be more frequent in EOCRC, which may be associated with genetic instability in tumors. Furthermore, EOCRC tumors have been reported to have distinct epigenetic characteristics with a lower prevalence of CpG island methylation. For example, the methylation level of long-interspersed nucleotide element 1 was particularly low in a previous study,[16] which is a type of post-translational modification that leads to gene silencing and represents another pathway in colorectal cancer tumorigenesis.

In terms of specific gene mutations, Bonjoch *et al*[17] found that some patients with CRC may develop the disease due to *BMPR2* mutations that disrupt the bone morphogenetic protein pathway, leading to increased cell proliferation. Recent research found that EOCRC exhibited a higher tumor mutation burden and greater tumor immune infiltration compared to late-onset colorectal cancer due to *LMTK3* mutations.[18] Lieu *et al*[19] found that *TP53* and *CTNNB1* mutations were more common in EOCRC, while mutations in genes such as *APC*, *KRAS*, and *BRAF* were more common in late-onset colorectal cancer. Compared to late-onset colorectal cancer, EOCRC had a higher proportion of non-silent mutations in *TP53*, *LRP1B*, and *TCF7L2* in somatic cells.[20] *TP53* gene mutations can impair tumor suppression and genomic stability, promoting cancer development and progression, and were found to be associated with poor prognosis in overall colorectal cancer.[21] The *APC* gene is a tumor suppressor gene, and mutations in *APC* usually result in abnormal activation of the Wnt signaling pathway, leading to abnormal proliferation and malignant transformation of intestinal mucosal cells.[22] *BRAF* gene mutations were closely associated with poor outcomes in colorectal cancer.[23] In sporadic EOCRC, another study reported that the prevalence of *TP53* gene mutations was similar to that in overall CRC patients, while the incidence of *APC* and *KRAS* mutations in sporadic EOCRC was lower than in overall colorectal cancer.[24] In summary, mutations in the *APC*, *TP53*, and *KRAS* genes have been found in both EOCRC and late-onset colorectal cancer, and any differences may lie in the distinct DNA methylation patterns between the two groups. Studying the specific mutated genes and genetic variation in EOCRC may provide directions for precision oncology treatment.

Immunity, gut dysbiosis, and EOCRC

Current research has found that the immune microenvironment of EOCRC differs from that of late-onset colorectal cancer, and these differences do not seem to be merely the result of age-related immune changes.[25] The increased levels of immune genes such as *C7*, *CFD*, and *SAA1*, which are associated with intestinal inflammation, suggest that the immune microenvironment of EOCRC may be pro-inflammatory and tumor-promoting due to immune dysregulation. Meanwhile, a study by Ugai *et al*[26] found that EOCRC tumors may exhibit lower levels of tumor-infiltrating lymphocytes. Recently, a study reported that the T-cell receptor diversity in EOCRC tumors is higher than in late-onset colorectal cancer, suggesting a more diverse intratumoral T-cell response to tumor antigens.[27] These findings collectively indicate that immunity might play an important role in the development and progression of EOCRC. Bacteria, through their toxins, can increase intestinal barrier permeability.[28] This may allow bacteria and bacterial components to cross the gut wall into the bloodstream. When gram-negative bacterial components, such as lipopolysaccharide (LPS), enter the blood, they can activate an inflammatory cascade by binding to Toll-like receptor 4 (TLR4) on immune cells. This stimulates the release of pro-inflammatory cytokines and chemokines, affecting gut immunity and influencing the development of colorectal cancer.[28] Gut microbiota dysbiosis leads to an imbalance in the gut immune microenvironment, which can contribute to the development of EOCRC. In contrast, probiotics help prevent and treat EOCRC by regulating the immune system, inhibiting cancer cell proliferation, restoring microbiota balance, producing anticancer agents, repairing gut barriers, and reducing carcinogenic substances.[29] A large number of laboratory studies have studied the relationship between colorectal cancer and intestinal flora disorder and immune abnormality,[30–33] which are considered to play an important role in the pathogenesis of colorectal cancer. Although EOCRC shares a certain degree of similarity in pathogenesis with overall colorectal cancer, some specific aspects of gut dysbiosis, gut immunity, and the pathways involved in the development of EOCRC still require further research.

Environmental Risk Factors for EOCRC

Lifestyle factors associated with EOCRC

EOCRC risk is also influenced by lifestyle factors, including smoking, alcohol consumption, dietary habits, and sedentary behavior [Figure 1].

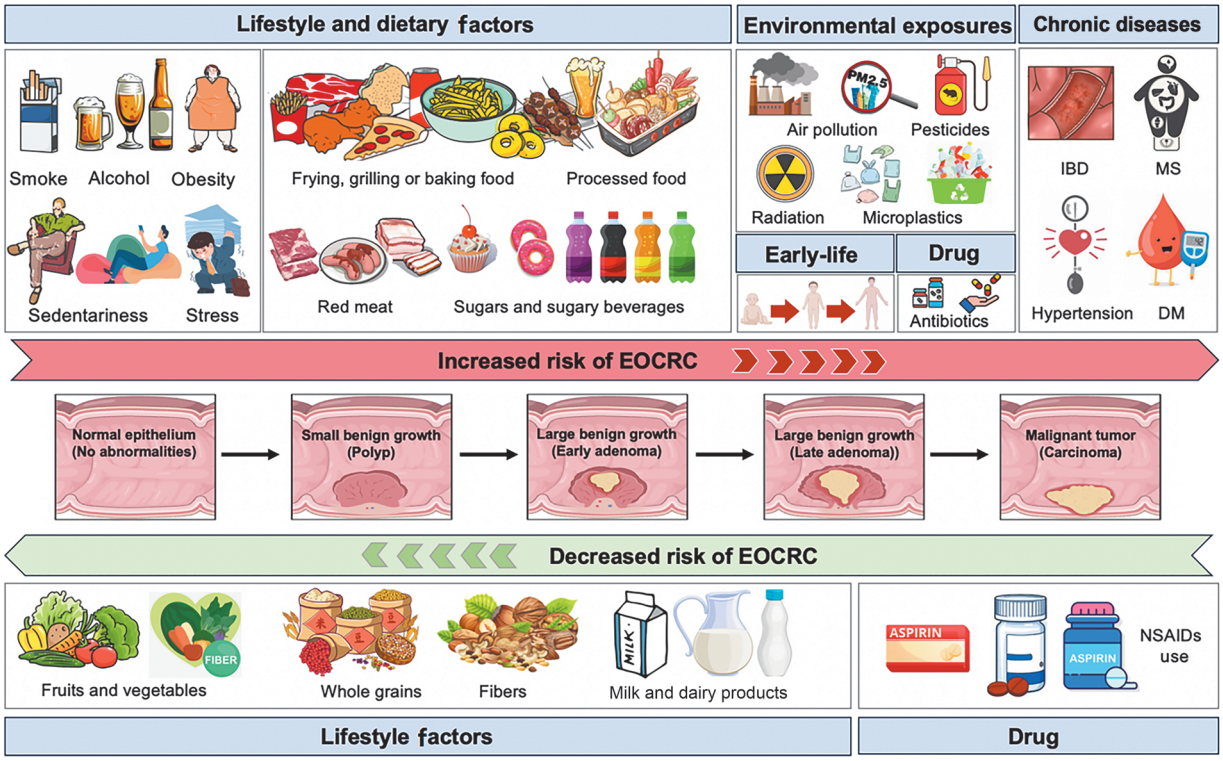

Figure 1: Environmental factors related to early-onset colorectal cancer. DM: Diabetes mellitus; EOCRC: Early-onset colorectal cancer; IBD: Inflammatory bowel disease; MS: Metabolic syndrome; NSAIDs: Non-steroidal anti-inflammatory drugs.

Recent meta-analyses by Zhang *et al*[5] and Hua *et al*[34] in 2023 have demonstrated that smoking is a significant risk factor for the development of EOCRC. In particular, it has been shown that current smokers exhibit a statistically significant 1.6-fold increased risk of EOCRC, ranking highest among all risk factors.[5] Jung *et al*[35] conducted a study on smoking (categorized as never smokers, <20 pack-years, and ≥20 pack-years), and reported a dose–response effect of smoking on the risk of colorectal neoplasms in individuals aged 30 to 39 years and 40 to 49 years. Specifically, compared to non-smokers, in individuals aged 30 to 39 years, those with a smoking history of less than 20 pack-years and exceeding 20 pack-years had a higher risk of colorectal neoplasia, with ORs of 1.43 (95% CI: 1.23, 1.66) and 1.93 (95% CI: 1.34, 2.77), respectively; in individuals aged 40 to 49 years, the ORs were 1.16 (95% CI: 1.03, 1.31) and 1.54 (95% CI: 1.33, 1.78), respectively. Existing research suggests that smoking contributes to EOCRC through mechanisms like chronic inflammation, DNA damage, immune system alterations, and disruption of the gut microbiome. However, in a study of Chinese population aged 30–50 years, no relationship was found between smoking and the risk of EOCRC.[36] Given the inconsistency in the current evidence regarding the relationship between smoking and EOCRC risk, well-designed prospective cohort studies across different ethnicities, regions, and countries are needed to better clarify the association between smoking and EOCRC.

Furthermore, alcohol consumption is significantly associated with an elevated risk of EOCRC. A large population-based study found that excessive alcohol consumption is associated with an increased risk of EOCRC.[37] A study in 2023 further confirmed that moderate drinkers (adjusted hazard ratio [aHR], 1.09 [95% CI, 1.02 to 1.16]) and heavy drinkers (aHR, 1.20 [95% CI, 1.11 to 1.29]) showed a significantly increased risk of EOCRC compared with light drinkers.[38] There was also a significant dose–response relationship between alcohol consumption frequency and EOCRC risk. Compared to non-drinkers, the risk increased by 7%, 14%, and 27% for individuals who drank 1–2 days, 3–4 days, and ≥5 days per week, respectively.[38] Although the precise mechanisms remain largely elusive, dysbiosis of the gut microbiota is believed to contribute to this increased risk, potentially leading to inflammation and exposing the colonic epithelium to carcinogenic alcohol metabolites. This exposure may induce DNA damage within the colonic epithelium, representing potential pathways to carcinogenesis.

Furthermore, dietary habits could play an important role in the development of EOCRC. Existing literature consistently underscores that a Western dietary pattern, characterized by high consumption of red meat, fats, sugars, and low fiber, serves as a significant risk factor for EOCRC.[34] A recent prospective cohort study found that diets rich in sulfur-metabolizing microbes are also associated with an increased risk of EOCRC precursors.[39] Conversely, high consumption of fruits and vegetables, whole grains, and dairy products is associated with a reduced incidence of EOCRC.[40] Western cooking methods, such as frying, grilling, or baking, generate advanced

glycation end products that foster oxidative stress and chronic inflammation, thereby creating a microenvironment conducive to the development of EOCRC.[41] Processed foods and red meat contain carcinogenic compounds such as N-nitroso compounds, polycyclic aromatic hydrocarbons, and heterocyclic aromatic amines. These compounds contribute to the increased risk of EOCRC by exerting direct carcinogenic effects on the colonic epithelium and inducing inflammation-driven malignancies, which promote abnormal cell proliferation and the development of cancer. Moreover, the consumption of sugar in a Western-type diet is linked to increased EOCRC risk. A large American cohort study in 2021 found that a higher intake of sugar-sweetened beverages during adulthood and adolescence is associated with an increased risk of EOCRC in women. Women who consumed two or more servings of these beverages daily had a significantly higher risk of EOCRC compared to those who did not.[42] Similarly, higher total fructose intake during adolescence is positively correlated with the risk of early-onset rectal adenoma[43] Several mechanisms potentially explain how sugar intake promotes colorectal cancer development. High sugar consumption may directly influence the gut microbiome, contributing to EOCRC by inducing insulin resistance, obesity, and type II diabetes. Furthermore, fructose generates advanced glycation end products, which, as previously mentioned, play a significant role in carcinogenesis.

Sedentary behavior has recently been identified as a novel environmental risk factor for EOCRC. A prospective study found that sedentary television viewing for more than 1 hour is associated with a 12% increased risk of colorectal cancer, and viewing for more than 2 hours is associated with a 70% increased risk, especially in the rectal area.[44] Lack of physical activity may lead to reduced energy expenditure, increased calorie intake, and unhealthy dietary consumption. Notably, increased sedentary time may be associated with obesity. As a well-established risk factor for EOCRC, numerous recent studies have consistently demonstrated a strong association between obesity and EOCRC.[45] Furthermore, recent evidence from Germany suggests that overweight and obesity, even from early adulthood, play a crucial role in the risk of EOCRC.[46]

At the molecular and clinical levels, although the mechanisms linking obesity and EOCRC remain partly understood, it is hypothesized that an interaction exists between obesity, estrogen levels, and colorectal cancer risk, with obesity acting as a driver of chronic inflammation.[47] Obesity may serve as an independent risk factor, while also being influenced by other established colorectal cancer risk factors, including sedentary lifestyle, lack of physical activity, low dietary fiber intake, heightened insulin resistance, and stress.

Perceived stress, defined as an individual's perception of social and psychological stress, not only heightens the risk of rectal cancer but also elevates the likelihood of offspring developing colorectal cancer if experienced during pregnancy.[48] Currently, much evidence supports its importance as an environmental risk factor for EOCRC, including the consistency between the global perception of stress increase and the rising trend of EOCRC.[49] Moreover, stress-induced alterations to the inflammatory environment, innate immunity, immune cell function, and the microbiota may promote the development of EOCRC. Therefore, it is essential to consider the biological effects of stress and stress mediators on the mechanisms underlying disease progression in EOCRC populations.[50]

Environmental exposures associated with EOCRC

Certain environmental exposures may play a significant role in the development of EOCRC, such as exposure to environmental pollutants like air pollution, pesticides, radiation, and microplastics [Figure 1]. With the accelerated global industrialization process, air and other environmental pollutants have been found to be associated with the occurrence and development of many chronic diseases, including colorectal cancer.[51] Previous studies have shown that prolonged exposure to fine particulate matter (PM2.5) and toxic metals can generate reactive oxygen species (ROS) and trigger systemic inflammation, both of which play a role in the development of colorectal cancer.[52] A study from Thailand[53] involving 59,605 patients investigated the spatial and temporal association between air quality and colorectal cancer incidence from 2010 to 2016. The results showed that with every 10 $\mu g/m^2$ increase in the relative risk levels of black carbon, organic carbon, and dust-$PM_{2.5}$, the risk of colorectal cancer increased by 4%, 4%, and 15%, respectively. The risk of colorectal cancer significantly increased with the accumulation of ambient air pollution. The risk of colorectal cancer has disproportionately increased in countries with less stringent environmental regulations, particularly in regions with high pesticide use and air pollution levels. Studies have shown elevated pesticide levels in the serum of CRC patients.[53] Moreover, radiation exposure is also associated with an elevated risk of EOCRC, which can originate from environmental or occupational exposures. In addition, microplastics are increasingly entering human consumption cycles and the food chain.[54] Their association with EOCRC may relate to dysbiosis and gut irritation.[55] A study analyzing tumor biopsies from colorectal cancer patients observed a higher presence of microplastic particles in tumor tissues compared to non-tumor colon tissues in healthy controls.[56] However, the precise mechanisms by which microplastics disrupt the mucosal barrier and elevate the risk of EOCRC require further elucidation.

Early-life exposures

Adult exposure to established risk factors cannot fully account for the increase in EOCRC incidence beginning in the 1980s, nor the pronounced birth cohort effects observed in epidemiological studies[57] [Figure 1]. Global dietary changes began around the 1950s, marked by increased consumption of processed meats, fast food, cooking oils, high-fructose corn syrup, and sugar. The adenoma-carcinoma sequence between exposure and colorectal cancer can have a latency period spanning decades. Therefore, early life exposures are increasingly

suspected to be risk factors for EOCRC, with supporting evidence from periods of fetal development, childhood, adolescence, and early adulthood.[57] Obesity, particularly during childhood, is recognized as a major risk factor for EOCRC. Analyses of the Nurses' Health Study II (NHS2) data[58] and a German prospective cohort study[59] demonstrate that obesity during childhood and adolescence is associated with an increased risk of subsequent colorectal cancer. Increased body fat has been shown to elevate colorectal cancer risk. Furthermore, the NHS2 results indicated that adolescent dietary patterns, including intake of meat, fish, dairy, and sugar beverages, also elevate EOCRC risk.[58] Interestingly, Peeri *et al*[60] study suggested a correlation between the number of older biological siblings and the risk of developing EOCRC, which could potentially have been mediated by advanced parental age and early antibiotic exposure. A nationwide case–control study based on the Swedish population found that women who had a cesarean delivery had a higher likelihood of developing EOCRC compared to those who had a vaginal delivery, which may also be associated with early gut microbiome dysbiosis.[61] Meanwhile, Jiang *et al*[62] highlighted that antibiotic use during early life is associated with an increased risk of EOCRC and early-onset adenomas, with a pronounced effect in individuals carrying the rs281377 TT/CT genotype of *FUT2*. In contrast, the associations between early life factors such as birth weight, multiple births, breastfeeding during infancy, and age at menarche have not shown significant correlations with the risk of EOCRC.[62] The above-mentioned research evidence underscores the need for further studies on early-life exposures to better understand their relationship with EOCRC, particularly the interplay between these early-life exposures and genetics.

Antibiotics and aspirin use

The overuse of antibiotics is a global public health issue and is hypothesized to be a risk factor for EOCRC [Figure 1]. A nationwide cohort analysis from Sweden in 2021 indicated that antibiotic users have a higher risk of developing colorectal polyps compared to non-users (OR = 1.08; 95% CI: 1.04–1.13), with the risk increasing with the number of prescriptions.[63] Another cohort analysis of the same population in 2022 suggested a potential but moderate association between broad-spectrum antibiotic use and EOCRC (adjusetd odd ratio [aOR] = 1.13, 95% CI: 1.02–1.26).[64] Epidemiological studies have established the associations between antibiotic overuse and various diseases that may lead to EOCRC, including obesity, diabetes, and inflammatory bowel disease.[65] In the previous discussion, we mentioned that Jiang *et al*'s[62] study suggested that early-life antibiotic use is associated with an increased risk of EOCRC and early-onset adenomas. Antibiotic use during early life may lead to long-term changes in the gut microbiome and impair normal immune surveillance caused by immune-stimulating bacterial products. For example, adhesins expressed by *Fusobacterium nucleatum* bind immune receptors on immune cells, preventing cytotoxic activity against tumor cells and disrupting anti-tumor immunity. The association with adenomas is especially pronounced in individuals with the rs281377 TT/CT genotype of Fucosyltransferase 2 (*FUT2*), likely due to *FUT2* gene defects affecting gut microbiome structure and function, promoting inflammation and epithelial barrier damage.[62,66] In addition, the use of aspirin is considered a protective factor for EOCRC, with related studies showing a significant association between aspirin use and a reduced risk of EOCRC (OR = 0.66, 95% CI: 0.52–0.84).[67]

Chronic diseases associated with EOCRC

Previous studies have indicated that chronic diseases increase the risk of EOCRC [Figure 1]. Among these, inflammatory bowel disease (IBD), especially when diagnosed in childhood, has been shown to be a significant risk factor for EOCRC.[68] A large retrospective study demonstrated that IBD patients have a higher risk of EOCRC compared to the general population.[69] This risk increases with disease duration, the extent of colonic involvement, and the presence of other conditions like primary sclerosing cholangitis.[70] Metabolic syndrome, characterized by a cluster of risk factors including obesity, hypertension, dyslipidemia, and glucose metabolism abnormalities, is also associated with increased EOCRC risk. A meta-analysis published in 2023 strongly supported this association (OR = 1.29; 95% CI, 1.15–1.45).[34] A nested case–control study by Chen *et al*[71] in 2021 reported that metabolic syndrome patients have a 25% higher risk of developing EOCRC compared to controls. A large-scale cohort study in China indicated that hypertension (HR, 1.99; 95% CI: 1.04, 3.81) and diabetes (HR, 2.20; 95% CI: 1.08, 4.49) significantly increase the risk of EOCRC.[36] Follow-up results from a Swedish cohort study involving approximately 12.61 million residents showed that diabetic patients have a 1.9-fold higher risk of EOCRC compared to the general population (95% CI: 1.6–2.3).[72] As previously mentioned, common risk factors such as obesity and sedentary lifestyles could also contribute to this elevated risk. Although the precise mechanisms remain under investigation, some hypotheses propose that tumorigenesis may result from hyperinsulinemia and hyperglycemia, which could promote the growth and proliferation of colonic epithelial cells. Given the chronic diseases associated with EOCRC, further research is essential to comprehensively explore the specific characteristics of these conditions and their relationship to EOCRC development. This endeavor will facilitate the identification of high-risk individuals and contribute to the development of early detection strategies and interventions aimed at reducing risks for susceptible populations.

Interactions between Environmental and Genetic Factors of EOCRC

Modified GWAS, specifically focusing on gene-environment-wide interaction studies (GEWIS), have unveiled significant interactions with various environmental risk factors for EOCRC, encompassing diet, alcohol consumption, lifestyle choices, and medication use [Figure 2]. Meanwhile, the aforementioned environmental risk

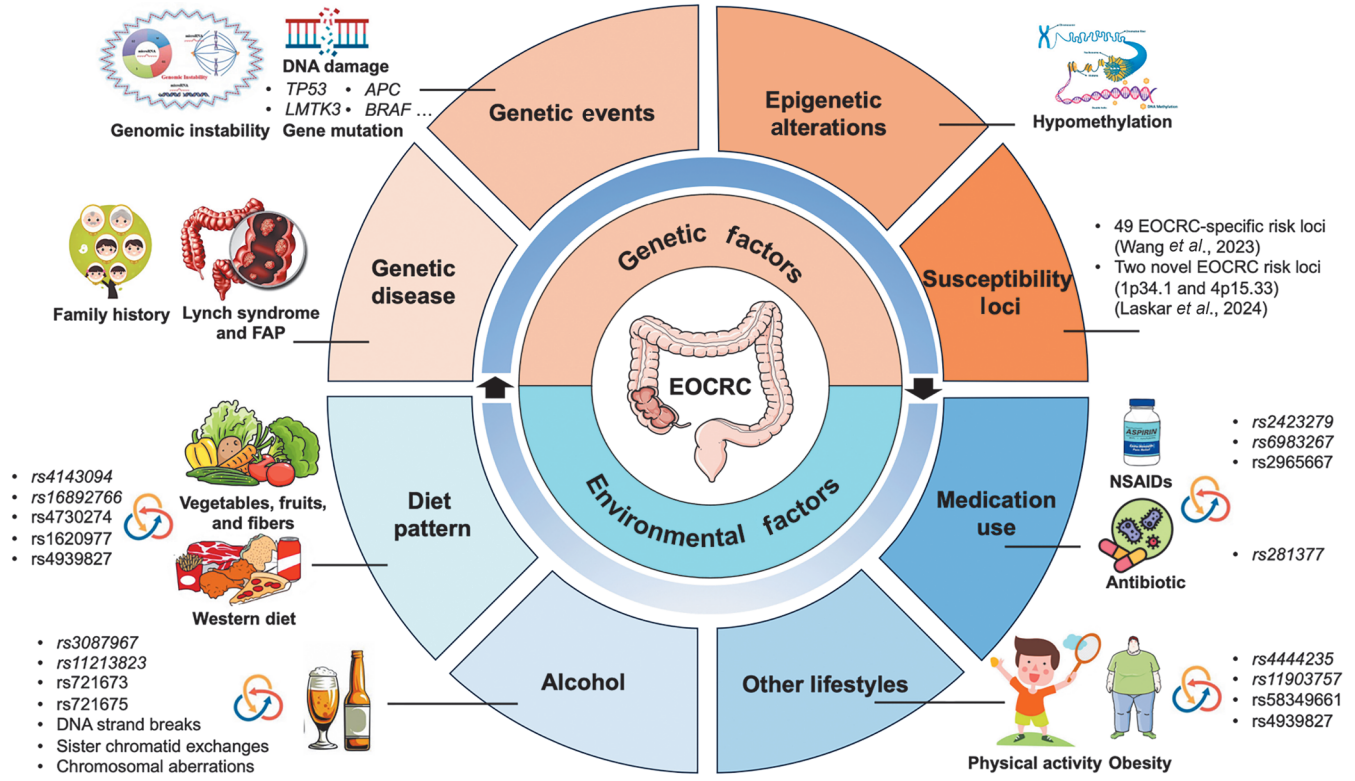

Figure 2: Genetics of early-onset colorectal cancer and its interaction with environmental factors. EOCRC: Early-onset colorectal cancer; FAP: Familial adenomatous polyposis; NSAIDs: Non-steroidal anti-inflammatory drugs.

factors are associated with known genetic mutations, epigenetic alterations, genomic instability, and genetic events such as DNA damage in colorectal cancer.

Diet and genetics

Dietary patterns and alcohol consumption have been shown to be associated with EOCRC. Recent findings from GWAS of EOCRC have revealed that many genetic variants interact with environmental exposures, collectively influencing disease occurrence. For instance, the rs16892766 locus at 8q23.3, near *EIF3H/UTP23* gene, interacts with vegetable consumption to impact colorectal cancer risk, with the SNP's main effect increasing with higher vegetable intake.[73] The rs4730274 locus near the *SLC26A3* gene shows a correlation with fiber consumption in colorectal cancer, while the rs1620977 locus near the *NEGR1* gene relates to fruit intake. Consumption of red and processed meat, known risk factors in Western diets for EOCRC, interacts with the genetic variation rs4143094 near the *GATA3* gene on chromosome 10p14, jointly affecting colorectal cancer risk.[74] In addition, the rs4939827 locus within the *SMAD7* gene is associated with the Mediterranean dietary pattern in colorectal cancer studies, with the TT genotype showing reduced colorectal cancer risk compared to the CC genotype.[75] Furthermore, alcohol consumption is a risk factor for EOCRC, with many studies observing the interaction between different genetic loci and alcohol intake. Moderate alcohol consumption is associated with reduced colorectal cancer risk in individuals with the rs9409565 CT genotype compared to non/occasional drinkers, whereas it is not associated with CC genotype patients.[76] Another study found that carrying the risk alleles of expression quantitative trait locus (eQTL, rs3087967) and metabolomic quantitative trait loci (mQTL, rs11213823) polymorphisms in *COLCA1/COLCA2* interacts with alcohol consumption, increasing colorectal cancer risk.[77]

Diet and alcohol consumption are well-established risk factors for EOCRC, but their specific associations with underlying genetic mechanisms remain unclear. Previous research suggests that a Western-style diet increases the risk of colorectal cancer, especially for distal tumors and those with specific molecular profiles like *KRAS*-wildtype, *BRAF*-wildtype, CpG island methylator phenotype-low, and microsatellite stability (MSS).[78] An additional study indicated that red and processed meat intake was less strongly associated with the risk of *KRAS*-mutated colorectal cancer than with *KRAS*-wildtype colorectal cancer.[79] Additionally, prudent dietary patterns–diets rich in fruits, vegetables, fish, poultry, and whole grains are linked to a lower colorectal cancer risk, regardless of tumor location or molecular subtype.[78] Meanwhile, a prudent dietary pattern has also been reported to significantly reduce the likelihood of a *KRAS2* rectal tumor mutation.[80] Considering that acetaldehyde, a genotoxic compound in alcohol, promotes the generation of ROS and reactive nitrogen species, leading to DNA strand breaks, sister chromatid exchanges, and chromosomal aberrations may contribute to the initiation and progression of colorectal cancer.[81] Therefore, alcohol consumption may also contribute to EOCRC through genetic damage as a potential pathway.

Physical activity, overweight, and genetics

The lack of physical activity and being overweight are both associated with an increased risk of EOCRC. A study involving 703 cases of CRC and 1406 healthy controls from the National Cancer Center in Korea revealed that the SNP rs4444235 at the 14q22.2 locus interacts with regular exercise, influencing colorectal cancer risk.[82] The risk allele (C) of rs4444235 reduced the risk of colorectal cancer in individuals who exercise regularly (OR = 0.58, 95% CI = 0.38–0.88) but increased the risk in individuals who do not exercise (OR = 1.47, 95% CI = 1.02–2.10).[82] Yang *et al*'s[83] study identified a nominally significant interaction between body mass index (BMI) and rs11903757 (2q32.3/NABP1) in colorectal cancer risk. The genetic locus rs58349661 in the *FMN1/GREM1* gene region interacted with BMI in colorectal cancer risk.[84] Another study reported a novel gene–environment interaction between female BMI and the *SMAD7* (rs4939827) intronic locus in colorectal cancer risk.[85] Interestingly, this locus was also associated with the Mediterranean dietary pattern mentioned earlier, indicating that the same genetic locus may interact with multiple environments, collectively influencing disease occurrence. It is intriguing that studies have shown high levels of physical activity to decrease the risk of *TP53* and *KRAS2* mutations in colorectal tumors.[80] EOCRC predominantly involves distal colon and rectal cancers, with the majority of distal cancers originating from traditional adenomas associated with molecular alterations like *TP53* mutations. This suggests that to some extent, maintaining regular physical activity can still reduce the risk of EOCRC associated with characteristic mutations.

Nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and genetics

The association between NSAIDs, antibiotics, and EOCRC has been widely discussed. There have been several studies on the relationship between aspirin and genetic susceptibility in the occurrence of colorectal cancer. An interaction between the SNP rs2423279 at 20p12.3 and aspirin use has been identified.[82] And a review reported the interaction between rs6983267 (8q24) and aspirin use.[86] Moreover, data from five case–control and five cohort studies conducted between 1976 and 2003 in the United States, Canada, Australia, and Germany reported a significant genome-wide interaction between the rs2965667 at chromosome 12p12.3 near the *MGST1* gene and the use of aspirin and/or NSAIDs. In addition, a significant genome-wide interaction was observed between the SNP rs16973225 at chromosome 15q25.2 near the *IL16* gene and the use of aspirin and/or NSAIDs.[87] In addition, for individuals with Lynch syndrome, taking 600 mg of aspirin daily for at least two years can reduce CRC risk by 63%.[88] Further research has found that in CRC cell lines with mismatch repair gene defects, aspirin, and sulindac enhance apoptosis in genomically unstable cells, thereby suppressing the microsatellite instability phenotype.[89]

The interaction between antibiotic use and genetics has also been reported to affect the occurrence of EOCRC. A study in 2023 indicated that long-term or repeated use of antibiotics in early life is associated with an increased risk of EOCRC and early-onset adenomas, with the association of adenomas being predominant in individuals with the rs281377 TT/CT genotype.[62]

Other factors and genetics

In addition to the factors mentioned above interacting with genetic susceptibility to colorectal cancer, studies using data from 31,318 cases of colorectal cancer and 41,499 controls found that genetic variants related to insulin signaling (*SLC30A8*) and immune function (*LRCH1*) (rs3802177, rs9526201) may alter the association between diabetes and colorectal cancer risk.[90] Furthermore, research has found a significant interaction between rs964293 at 20q13.2/CYP24A1 and exposure to estrogen and progesterone in female CRC patients.[91] Moreover, many studies have found interactions between gene polymorphisms and mutations in DNA repair genes and promoter activation in colorectal cancer patients,[14,92] further explaining the potential relationship between genetic susceptibility and tumor risk. However, currently, there are few studies directly investigating the interaction between susceptibility loci and environmental factors in the EOCRC population. Considering the rising trend of EOCRC, further research on the GWAS and environmental risk factors of EOCRC, as well as their interactions, may provide more accurate insights into its etiology.

Future Research Efforts and Implications

The rising incidence of early-onset EOCRC poses a significant public health challenge warranting immediate attention. This review underscores the multifaceted nature of EOCRC, highlighting the roles of genetic and environmental risk factors, as well as the impact of their interaction on the development and progression of EOCRC. Environmental risk factors, including lifestyle and dietary factors (obesity, smoking, alcohol consumption, sedentary behavior, processed foods, red meat, and sugars and sugary beverages), environmental exposures (air pollution, radiation, pesticides), chronic diseases (IBD, metabolic syndrome, diabetes), and early life exposures (antibiotic use), consistently correlate with increased EOCRC risk. In contrast, diets rich in fruit, vegetables, whole grains, dairy products, and NSAIDs use are associated with reduced EOCRC risk. Significantly, the higher prevalence of specific pathogenic germline variants in EOCRC patients underscores the imperative for early genetic screening. Current evidence suggests that sporadic EOCRC may be associated with mutations in *TP53*, *LRP1B*, *TCF7L2*, *CTNNB1*, *BRAF*, and *LMTK3*, as well as hypomethylation, although the results are not entirely consistent across different studies. Furthermore, the latest two EOCRC GWAS have yielded significant findings. The first study identified 49 genetic loci linked to EOCRC susceptibility, including rs12794623 which affects *POLA2* expression and promotes CRC.[12] Another study indicated new risk loci at 1p34.1 and 4p15.33 were found for EOCRC, along with a harmful variant (rs36053993, G396D) in the *MUTYH* gene associated with polyposis.[14] Mendelian randomization analyses from EOCRC

GWAS supported associations with higher alcohol consumption, obesity, and fasting insulin levels, potentially increasing EOCRC risk.[14]

The interaction between environmental and genetic factors in the process and mechanisms inducing EOCRC is intricate. Specific dietary patterns like the Western diet (high in red and processed meats) and the Mediterranean diet (high in fruits, vegetables, and fiber) interact with genetic loci to influence colorectal cancer development. Alcohol consumption interacts with genetic variants and could also result in genetic damage that promotes CRC. Insufficient physical activity and obesity interact with loci to collectively increase CRC risk, including EOCRC. NSAIDs are known for their preventive effects on CRC, interacting with genetic loci. Long-term antibiotic use in early life raises the risk of EOCRC and early-onset adenomas, particularly in individuals with specific genotypes.

Although existing GWAS studies have explained some of the interactions between environmental factors and genes, current research on various environmental exposures remains predominantly limited to epidemiological association studies, with insufficient focus on the specific effects of these factors. Drawing from current research,[30–33] gut microbiota dysbiosis and gut immunity may serve as key pathways through which environmental factors exert their pathogenic influence. EOCRC has a high degree of similarity in the pathogenesis with overall colorectal cancer. Prolonged exposure to environmental factors such as alcohol consumption, dietary habits, and antibiotic use may disrupt the gut microbiota, leading to intestinal metabolic and immune disturbances that ultimately trigger EOCRC. Investigating the precise changes in the composition and function of the gut microbiota and abnormalities in immunity could provide valuable insights into the distinct roles and mechanisms of these environmental factors.

Several limitations of the current research should be acknowledged. First, most existing large-scale EOCRC GWAS studies focus on European populations, predominantly white individuals. This highlights the necessity of conducting more research to generalize these findings to other populations and regions. Second, although environmental exposure factors in current study include data from different regional populations, enhancing the generalizability of the findings, it is important to note that differences in lifestyle habits across regions and ethnicities, along with variations in the definitions of these exposures across studies, pose challenges in making cross-regional comparisons on EOCRC risk factors. Third, the limited GWAS data on EOCRC hinders the study of gene–environment interactions. Fourth, despite existing research providing valuable clues, a clearer understanding of the pathogenic mechanisms of EOCRC will require more systematic basic and clinical studies for validation. Fifth, although current studies have included existing epidemiological studies on environmental factors in EOCRC, some of them are cross-sectional studies, which limits the ability to infer the temporal causality of EOCRC risk factors. More prospective cohort studies on EOCRC will be crucial for better exploring the underlying mechanisms and clarifying the relationships between environmental factors, changes in gut microbiota, and the development of EOCRC.

Addressing the challenge of EOCRC requires comprehensive public health strategies. Developing genetic chips to identify individuals at high genetic risk of EOCRC enables precise early detection and targeted interventions. By integrating genetic and environmental risk factors, personalized screening strategies can optimize screening age based on individual colorectal cancer risk profiles. This tailored approach overcomes the limitations of the current uniform screening age, facilitating the rational allocation of colonoscopy resources, reducing unnecessary invasive procedures, and improving the detection rate of colorectal lesions. Promoting healthy lifestyles, including a healthy diet, smoking cessation, alcohol moderation, and regular physical activity, will help reduce the risk of EOCRC. Developing probiotic-based interventions and preventing the misuse of antibiotics, especially during early life, are also crucial measures. In addition, improving both the natural and built environments, along with avoiding toxic and harmful pollutants, are also important public health strategies for preventing EOCRC. Future research can focus on long-term birth cohort studies and multi-omics research to better understand the risk factors of EOCRC. By precision medicine approaches, personalized prevention and screening strategies for high-risk individuals can be developed.

Conclusions

In conclusion, genetic and environmental factors, along with their interactions, play crucial role in the occurrence and development of EOCRC. Evidence concerning the etiology and mechanisms of EOCRC is rapidly accumulating, driven by advancements in large-scale EOCRC GWAS, extensive epidemiological studies, and comprehensive laboratory research. These investigations furnish substantial evidence that underpins the scientific foundation for the prevention and treatment of EOCRC.

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Conflicts of interest

None.

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