



## Early-onset colorectal cancer: Current insights and future directions

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### Abstract

Early-onset colorectal cancer (EOCRC) has seen an alarming rise worldwide over the past two decades. The reason for this global trend is poorly understood. EOCRC appears to have its own unique clinical and molecular features when compared with late-onset colorectal cancer. Younger patients appear to have more distal or rectal disease, a more advanced stage of disease at presentation, and more unfavorable histological features. Identifying risk factors for EOCRC is the first step in mitigating the rising burden of this disease. Here we summarize several noteworthy biological factors and environmental exposures that are postulated to be responsible culprits. This can hopefully translate in clinical practice to the development of better risk stratification tool for identifying high-risk individuals for early colorectal cancer screening, and identifying areas needed for further research to curb this rising trend.

**Key Words:** Early-onset colorectal cancer; Young-onset colorectal cancer; Risk factors; Environmental exposures; Microbiome; Genetics

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**Core Tip:** The incidence of early onset colorectal cancer is on the rise. Herein, we discuss on various risk factors that have been implicated for these recent trends and point to where future research needs to be directed for better utilization of healthcare resources. Early recognition and diagnosis are essential for better outcomes of this preventable cancer.

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer deaths worldwide. The International Agency for Research on Cancer estimated that there were 1.93 million new cases of CRC and 935000 deaths from CRC in 2020[1]. Early-onset CRC (EOCRC), largely defined as CRC occurring in adults younger than 50 years old, has seen an alarming rising trend in recent years[2-5].

A recent systemic review of 40 studies spanning 12 countries across five continents has found a nearly 30% increase in incidence of EOCRC around the world over the past 20 years, largely driven by increasing incidence in the United States, Australia, and Canada[6]. Since 1994, the incidence of EOCRC has been increasing by around 2% per year. This is alarming given that the overall incidence of and death from CRC has been on the decline[2]. An observational study done on CRC incidence in the United States population according to the Surveillance, Epidemiology, and End Results (SEER) registries found a steep increase in EOCRC incidence from age 49-50 years, with 92.9% of cases being invasive lesions picked up on screening[7]. This likely reflects that a significant proportion of the populations were screened too late, given that the goal of screening was to remove premalignant lesions to prevent malignant transformation. In 2018, the American Cancer Society (ACS) lowered their recommended age for average-risk adults to start screening at 45 years old[8]. Although this method allows early detection of advanced adenomas or CRC to reduce disease burden and mortality, this mass screening approach will likely lead to a substantial increase in cost and burden to the healthcare system.

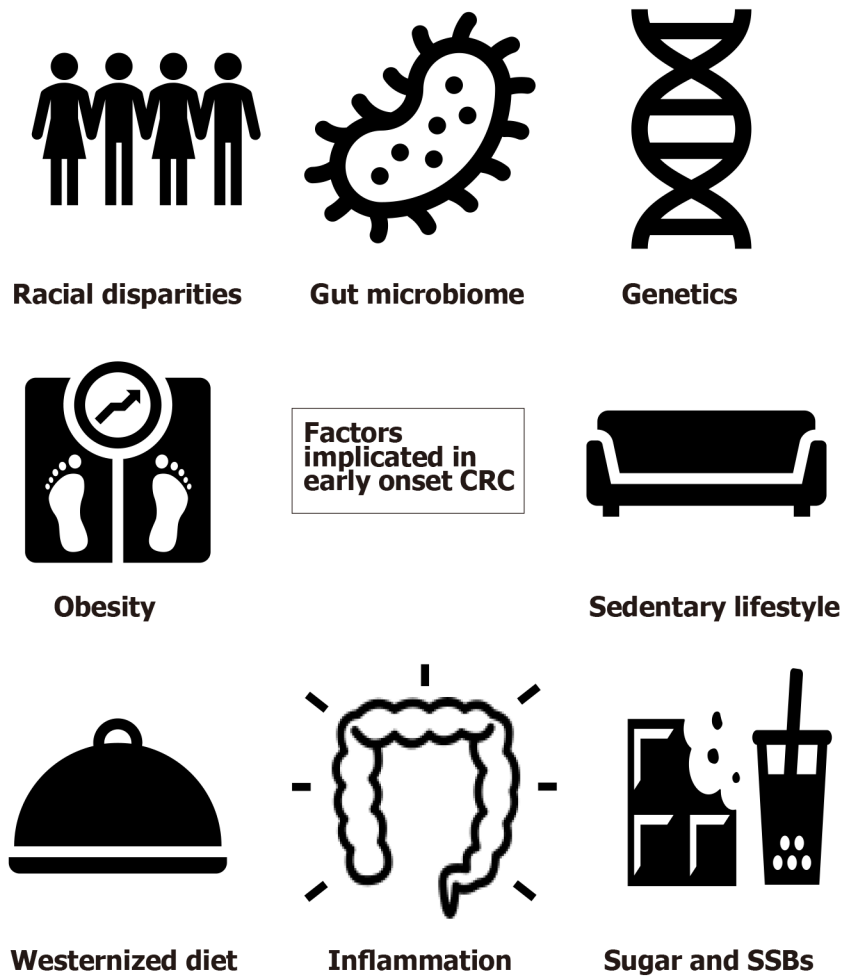
EOCRC tends to have a predominantly left colonic and rectal distribution, a higher proportion of mucinous and signet ring histologic subtype, poorer cell differentiation, a higher pathologic grade, and a more advanced stage at presentation[9-11]. Although hereditary cancer syndromes and family history account for approximately 30% of EOCRC cases, the majority appear to arise sporadically[12]. To date, the underlying etiologies of this rising trend have not yet been fully elucidated. Identifying specific risk factors or causes to this trend can allow for the establishment of better risk-stratification models and more targeted screening to tackle this global phenomenon.

Multiple postulated risk factors have been identified that may be driving factors to the development of EOCRC. Exposure to many potential elements from an early age from conception to adulthood may predispose to a higher risk of EOCRC. This includes external factors such as socioeconomic background, lifestyle, diet, and antibiotic exposure; and intrinsic factors, such as genetics, gut microbiota, and oxidative stress[13].

Apart from the well-established risk factors for CRC such as male gender, smoking, alcoholism, family history of CRC, type 2 diabetes, and inflammatory bowel disease, many studies have attempted to study additional demographic and environmental factors that may be specific risk factors for EOCRC[10,14,15]. A meta-analysis examining 20 studies through MEDLINE and Embase database search found that Caucasian ethnicity, obesity, and hyperlipidemia, as well as male gender, alcohol, and history of CRC in a first-degree relative, were all significantly associated with the development of EOCRC[16]. A more sedentary lifestyle or occupation, ulcerative colitis, hypertension, and diet-related factors were also found to have an association with increased risk in some studies[14]. Here we discuss in more detail some of the key suspects implicated in the development of EOCRC (Figure 1).

## RACIAL DISPARITIES

African Americans have been known to be at higher risk for the development of CRC compared with Caucasians, and this is usually associated with an earlier-onset and worse outcome[17]. Potential reasons for this disparity include lower socioeconomic status, limited access to healthcare, and lack of awareness of screening. Steps have



**Figure 1** Factors implicated in early-onset colorectal cancer. Image source for colon: <https://img.icons8.com>. CRC: Colorectal cancer; SSB: Sugar sweetened beverages.

been taken over the years to close this gap in CRC risk with the American College of Gastroenterology and American Society of Gastrointestinal Endoscopists guidelines recommending an earlier age to start CRC screening for African Americans[18].

These efforts have led to tangible results with the gap closing between Whites and Blacks[19]. In fact, the incidence of rectal cancer in Whites has now surmounted that of the Blacks and Hispanics in recent years, and the overall incidence of EOCRC is now similar in the two groups since 2015[2]. Results of a SEER analysis examining the difference in incidence of CRC amongst White and Black EOCRC patients from 1992-1996 to 2010-2014 showed that there was a 47% relative increase in CRC incidence in Whites, compared to a 1% relative increase in Blacks[20]. The rise in EOCRC is mainly due to an increase in rectal cancer, which was seen most strikingly in the White population. This suggests that rectal cancer may have its own distinct characteristics and etiological differences from colon cancer. Nevertheless, the incidence of EOCRC is still climbing steadily regardless of ethnicity, highlighting the need for further research into meaningful interventions to curb this rise.

## OBESITY AND SEDENTARY LIFESTYLE

Obesity has long been associated with an increased risk of CRC[21]. According to a recent propensity-weighted analysis which included 133008 adults diagnosed with EOCRC in the United States between 1999 and 2018, there was a strong association between EOCRC and a raised body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>, along with an earlier age of diabetes diagnosis[22]. A meta-analysis in 2017 found a 30% increased risk of CRC in men and a 12% increased risk of CRC in women for every 5 kg/m<sup>2</sup> increment increase in BMI[23]. There is also an increased risk of early-onset advanced adenoma amongst obese patients[24]. The underlying mechanism behind the

association between obesity and EOCRC is unclear, although it is postulated that there is an interplay between the risk of obesity, estrogen levels, and the risk of CRC, with obesity being a driver of chronic inflammation[25,26].

Of course, there are multiple confounding variables that may affect the relationship between obesity and EOCRC. This includes a reverse causality effect where CRC may induce weight loss. Obesity itself could also be a surrogate for other known risk factors for CRC. Metabolic syndrome, increased insulin resistance, raised insulin-like growth factor 1 (IGF-1), and raised low-density lipoprotein are all positively correlated with an increased risk for EOCRC[21,24].

Leading a sedentary lifestyle has also been recognized as an emerging global health problem due to increased desk work, the rising trend of e-commerce, and inactive media consumption since a young age[27]. A prospective study examining television viewing time (as a surrogate for sedentary time) in almost 90000 women aged 25 to 42 years in the United States found that more than 1 hour of daily TV viewing was associated with a 12% increased risk of CRC, particularly rectal cancer. More than 2 hours of TV viewing was associated with a 70% increase in risk. The risk appeared even higher in subgroups of patients with a high BMI, physical inactivity, and smokers [28].

Physical inactivity may result in lower energy use, higher caloric intake, and unhealthy dietary intake. It may also correlate with impaired glucose regulation or gut dysbiosis. Some studies have examined the role of increased physical activity to improve gut health by promoting certain bacterial species in the gut microbiome[29-31]. All in all, this highlights the importance of physical activity and controlling the obesity pandemic to prevent EOCRC.

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## WESTERN DIET

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A growing adoption of a non-Mediterranean, Western diet worldwide has been consistently shown in the literature to be an important risk factor[32,33]. A diet high in red, processed meat, and low in fibre from a young age has been shown to affect the gut microbiota and drive inflammation processes[34-36]. Westernized cooking methods, such as deep-frying, grilling, or roasting, generate more advanced glycation end-products (AGEs), which are complex compounds produced from food that is rich in fat and protein[37,38]. They are involved in promoting oxidative stress and chronic inflammation, which in turn promote a microenvironment favorable for colorectal carcinogenesis. Many studies have shown that AGEs are responsible for signal pathways involved in colitis-associated colorectal carcinogenesis seen in inflammatory bowel disease[39]. Mediterranean food, on the other hand, has low AGE levels and has been found to be protective against the development of CRC[40-42].

A recent prospective cohort study, which examined dietary patterns in 29474 women who underwent colonoscopy at < 50 years of age, found that a Westernized diet was positively associated with high-risk distal or rectal adenomas, whereas healthier diets such as a prudent diet, Dietary Approaches to Stop Hypertension, Alternative Mediterranean Diet, and Alternative Healthy Eating Index were inversely associated with early onset adenomas[43]. Interestingly, some studies have found that the genetic composition of tumors associated with a Western diet tends to be KRAS wild-type, and BRAF-wild type[44]. These genetic compositions are consistent with the typical features of EOCRC.

A meta-analysis recently published suggested a strong association of higher intake of dietary fibre, calcium, and yoghurt with a reduced risk of CRC, with convincing evidence that intake of a Western diet and processed meat is associated with a higher risk of EOCRC[45]. Interestingly, the impact of yoghurt and calcium may be related with the modulation of the gut microbiome, such as the presence of lactic acid-producing bacteria, which may reduce the level of carcinogens in the gut. Yoghurt also creates a lower pH in the colon, which may be more accommodating for probiotics [46]. This supports the idea that modulating the gut microbiome with prebiotics and/or probiotics may have a potential role in preventing the development of CRC, which will be further discussed in a later section.

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## SUGAR

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One of the other culprits in the plethora of Western food that may be a culprit for EOCRC is sugar. Refined sugars (including glucose, fructose, sucrose, and maltose) are

cheap and widely available worldwide. Sugar consumption in the form of snacks, desserts, sweets, or sugar-sweetened beverages has steeply increased especially during childhood and adolescence. Over the last decade, sugar consumption globally has grown from 154 to 171 million metric tons from 2009/2010 to 2019/2020[47]. This climb was found to be most significant in developing or low-income countries[48]. In a large United States cohort study that analyzed 95464 female registered nurses' dietary habits from the Nurses' Health Study II, it was found that high sugar (especially fructose) intake during adolescence was significantly associated with an increased risk of colorectal adenomas. Consuming two or more, rather than one, sugar-sweetened beverages a day in adolescence further increased the risk of EOCRC by two-fold[49].

Several mechanisms that tie sugar intake to the development of CRC have been postulated. High intake of sugar can promote obesity, insulin resistance, and type 2 diabetes[50,51]. Sugar, specifically fructose, may have a direct effect on the gut microbiome, leading to chronic inflammation and a heightened susceptibility of the colorectal epithelium to cellular damage[52]. Fructose also produces AGEs, which as previously discussed, has a potentially significant role in carcinogenesis[53]. Hyperinsulinemia and elevated IGF-1 levels can stimulate cell proliferation and differentiation, inhibit apoptosis, and in turn enhance tumor development. As adolescence is a period of pronounced physiological changes that include decreased insulin sensitivity and hyperinsulinemia, this stage of development may be particularly susceptible to the effects of a high sugar intake[49].

The link between diet, nutrients, and the pathogenesis of EOCRC is complex, with a myriad of processes involving immune signaling, genetic predisposition, and alterations in the gut microbiome. Other significant food exposures that may play a role in CRC include dietary additives, nitrate-containing foods, synthetic food colorings, monosodium glutamate, etc.[13,54]. Further studies on dietary causation links will bring to light any potential preventative measures for EOCRC.

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## GUT MICROBIOME

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It is estimated that 100 billion bacteria reside in the gastrointestinal tract (with a large proportion present in the colon), maintaining a symbiotic relationship with the human host[55]. The gut microbiota maintains gut homeostasis and functions and is often considered the first line of defense against pathogens. The composition of the gut microbiome is dynamic and subject to change by multiple factors throughout our lives. The first 1-2 years of life are pivotal for the development of the gut microbiota[56]. From birth, the microbiota composition is believed to differ significantly depending on the mode of delivery. Vaginally delivered babies tend to have more *Lactobacilli*, whereas Caesarean-delivered babies tend to have delayed colonization of facultative anaerobes such as *Clostridium*[57]. Breast-fed and bottle-fed babies also have markedly different gut microbiota composition, with breastfed babies having a much higher abundance of bacteria that are thought to be beneficial, such as *Bifidobacterium* and *Lactobacillus* species[58]. The composition of the gut microbiota stabilizes in early adulthood, but is still influenced by exposures such as diet, antibiotics, stress, and inflammation. The gut microbiome is responsible for the synthesis of many important vitamins or molecules for our human body, such as butyrate, folate, biotin, and cobalamin[59]. Some of these molecules are important in reducing bacterial translocation and promoting anti-inflammatory properties, and are essential in maintaining gut barrier integrity[60].

Alterations of gut microbiome composition (or gut dysbiosis) can lead to dysregulation of multiple pathways in the body. Extensive or prolonged antibiotics use can destroy normal gut flora and lead to colonization of unwelcome pathogens. Several microorganisms, such as *Streptococcus bovis*, *Bacterioides fragilis*, *Salmonella enterica*, *Fusobacterium*, and *Escherichia coli*, have been discovered to have a role in colon carcinogenesis. These pathogens can promote gut inflammation, produce cancer-associated metabolites, and activate oncogenic signaling pathways[61]. Chronic inflammation from bacterial infection or inflammatory bowel disease can cause epithelial barrier dysfunction and weaken host defenses. Different dietary exposures can lead to significant shifts in the gut microbiome, favoring organisms capable of utilizing those specific nutrients. High-fat diets can lead to accumulation of lipopolysaccharides that can promote inflammation and increase VEGF-C expression, which is a key regulator for lymphangiogenesis and lymph node metastasis in CRC[62]. One study found that a drastic increase in fibre intake over 2 wk led to a change in microbiome composition to fibre-degrading bacteria, such as *Bifidobacterium* and

*Lactobacillus*, which has been associated with anti-oncogenic properties[63-65].

Probiotics have long been marketed to the general public as a dietary supplement for their potential beneficial effects on the gut[66]. The replenishment of beneficial intestinal microbial communities may help stimulate epithelial cell proliferation, reduce pathogenic overgrowth, ameliorate gut inflammation, and potentially reduce the risk of CRC[67-69]. Studies have also shown that certain strains of probiotics may be effective as an adjuvant agent to CRC treatment[70]. Yet, its effects specifically on CRC treatment are not well studied and further investigation is required.

Our diet from birth has a role in shaping our gut microbiome. Understanding the relationship between diet and gut dysbiosis teaches us that how we shape our diets at an early age could impact the development of CRC. Thus, it is important to encourage healthy eating habits from childhood to maintain a healthy microbiota. Nevertheless, it remains difficult to prove the causative link between dysbiosis in early human development and its association with EOCRC, and further research in this area is needed.

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## GENETIC FEATURES

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Recognizing genetic alterations that can predispose to early onset of high-risk adenoma or CRC is crucial for deciding on early screening regimes and therapeutic strategies. Around 28% of EOCRC patients have a positive family history[71]. Patients with a first-degree relative of CRC have up to a four-fold increased lifetime risk of CRC[72]. Those with a known family history of a high-penetrance hereditary cancer syndrome, such as Lynch syndrome or adenomatous polyposis coli (APC), are at a particularly high risk and require an onset of colonoscopy screening at a much earlier age than the general population[73,74]. For non-hereditary cases, according to the ACS guidelines, those with a first-degree relative of CRC diagnosed before age 60 should also start colonoscopy screening from age 40, or 10 years younger than the earliest diagnosed relative[72]. However, low adherence to early screening guidelines is one of the major obstacles in EOCRC prevention. A study of 2473 patients with EOCRC found that family history-based early screening criteria were only adhered to in 25% of cases, and nearly all these patients could have had CRC diagnosed earlier or even prevented had they followed these guidelines[75]. This highlights the importance of public education on cancer screening programs.

Several studies have found that a significant proportion of EOCRC patients carrying a genetic mutation have no family history of CRC[10,71]. Apart from the well-recognized hereditary cancer syndromes accounting for around 13% of EOCRC cases, a wide spectrum of low to moderate penetrance sporadic mutations have recently been found in these patients, including some genes not traditionally associated with CRC [71,76]. A genome-wide association study found up to 140 single nucleotide polymorphisms associated with CRC[77]. Genetic mutations are much more common in EOCRC compared with those diagnosed at a later age[78] and may have a cumulative effect. However, in the absence of a positive family history, a proportion of these patients will not be enrolled into early screening programs with strategies to identify such patients being an unmet need[79].

The pathogenesis of CRC involves a complex sequence of multistep genetic alterations. There are three main genetic pathways of CRC carcinogenesis: Chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) pathways[80]. Each pathway is associated with specific genetic and epigenetic alterations. The CIN pathway is characterized by an accumulation of mutations in the tumor-suppressor and oncogenes, including *APC*, *KRAS*, and *TP53* amongst others, accounting for 85% of sporadic CRC cases. The MSI pathway, on the other hand, is a state of genetic hypermutability due to impaired DNA mismatch repair (MMR). MSI is the hallmark of Lynch syndrome-associated tumors, an autosomal dominant disorder characterized by the presence of DNA MMR genes (*e.g.*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*), accounting for around 8% of EOCRC cases[71,81]. Lynch syndrome increases the lifetime risk of CRC to 52%-82% depending on the pathogenic variant involved[82]. The CIMP pathway and BRAF V600E mutation are thought to be the molecular hallmark of the serrated pathway and are usually associated with proximal lesions[83].

EOCRC has distinct genetic features compared with late-onset CRC. A retrospective review of around 36000 CRC patients comparing genetic characteristics in different age groups showed that EOCRC patients are more likely to be MSI and have CTNNB1, ATM mutations, and CIMP hypermethylation. The consensus molecular subtype 1

was the most common CRC subtype in patients younger than 40 years old. There were fewer BRAF V600 mutations (< 4%) in patients less than 30 years old. KRAS, NRAS, and BRAF mutations in the mitogen-activated protein kinase pathway were lowest in the 18-29-year-old group (48%), and highest in the 70-year-old or older group (65%-70%)[84]. Hypermethylation of *ESR1*, *GATA5*, and *WT1* genes were also found to be suggestive of earlier diagnosis of CRC[85].

Certain genetic mutations may infer a higher rate of progression or be predictive factors for treatment resistance. KRAS mutation confers resistance to anti-EGFR therapy. Several studies have demonstrated that MSI tumors have a lack of response to 5FU-based chemotherapy[86]. Given that around 1 in 5 patients with EOCRC have a germline mutation, broad germline testing should be considered for all EOCRC patients to guide treatment modalities, prognostication, counselling to family members, and chemoprevention strategies[76,87].

Establishing a good predictive model for risk stratification of many genetic variants predisposing to CRC is important for more targeted screening of high-risk patients. A study using a polygenic risk score (PRS) derived from 95 common genetic variants was able to predict the risk of EOCRC when testing 12197 early-onset CRC and 95865 late-onset CRC patients of European descent. A higher PRS is more strongly associated with EOCRC than late-onset patients. Those in the highest PRS quartile had a 3.7-fold increased risk of EOCRC compared with those in the lowest quartile. Interestingly, high PRS cases also had a tendency towards distal and rectal tumors[78]. PRS may therefore be a useful tool to stratify risk when used alongside the identification of other lifestyle and environmental risk factors, and may pick up some high risk patients within the average-risk screening group who would otherwise have not been identified based on conventional criteria. This may provide a more targeted and personalized approach for CRC screening than our current standard of care.

## CONCLUSION

CRC is a genetic and molecularly heterogeneous disease. EOCRC represents a subgroup of CRC with unique characteristics. Genetic predisposition and multiple risk factors are being explored as potential contributors to this rising trend. Given the long process of transition from non-neoplastic cells to malignancy, exploring early-life exposures as potential culprits is important[13]. Increasing evidence has shown that obesity, sedentary lifestyle, Westernized diet, and high sugar intake are significant risk factors for EOCRC. Exposures as early as in the prenatal or perinatal stages of life, such as maternal diet or delivery methods, have been postulated to affect the composition of the gut microbiota. However, studies that prove causality remain elusive. Large epidemiological studies are still needed to further discover or verify potential causative factors.

The relationship between diet, lifestyle, and gut dysbiosis and their respective roles in colorectal carcinogenesis are complex. The composition of gut microbiome is dynamic and dependent on multiple factors including race, age, lifestyle, diet, medication use, stress, *etc.* There is currently no clear consensus for the definition of gut dysbiosis due to the high microbial heterogeneity in CRC[88]. Further investigations on the gut microenvironment from stool samples in CRC patients may help characterize the gut microbiome that predisposes to CRC, with emerging evidence that shows promise for its use in CRC screening and risk stratification. Future research on manipulating the gut microbiome through diet or drugs like probiotics may even play a role in cancer prevention.

Apart from the need for further research on exploring the unanswered questions of the underlying cause and mechanisms behind EOCRC, numerous barriers to the reduction of the incidence of EOCRC still exist. Poor compliance with early screening programs may be due to inadequate public awareness[89]. Information on family history may not be known to patients. Young patients and physicians alike tend to attribute early symptoms to non-sinister pathologies that may result in a delay of diagnosis. A study of young patients has shown that they present to a medical practitioner on average 294 d after the onset of rectal bleeding, which likely resulted in a more advanced stage of disease[90]. With regard to healthcare systems, there may be access, cost, or policy barriers to screening and treatment.

Steps to fight EOCRC include raising awareness of this growing threat through education and public promotion. This includes public awareness campaigns, educating the public on the dietary or lifestyle risks of CRC, and enhancing physician awareness of EOCRC. Advising young patients to stay vigilant of early symptoms,

such as per-rectal bleeding, abdominal pain, weight loss, and change in bowel habits and to seek timely medical attention is also important. Promoting awareness of early colonoscopy screening for high-risk groups, and referring patients who are eligible for genetic counselling and testing are essential for early identification of at-risk individuals. Further research on predisposing genetic and epigenetic signatures is needed. In the future, we should strive for specific genetic profiling through whole-genome sequencing for better risk stratification[91]. It may be useful to see how well specific risk stratification tools including lifestyle risks or PRS perform in the real world to identify high-risk patients for a more personalized screening strategy, which in turn may allow for better allocation of resources to those most in need to combat this global rise in EOCRC.

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