Field synopsis of environmental and genetic risk factors of sporadic early-onset colorectal cancer and advanced adenoma

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Abstract

Background: To systematically appraise and synthesize available epidemiological evidence on the associations of environmental and genetic factors with the risk of sporadic early-onset colorectal cancer (EOCRC) and early-onset advanced colorectal adenoma (EOCRA).

Methods: Multiple databases were comprehensively searched to identify eligible observational studies. Genotype data from UK Biobank were incorporated to examine their associations with EOCRC in a nested case-control design. Meta-analyses of environmental risk factors were performed and the strength of evidence was graded based on predefined criteria. Meta-analyses of genetic associations were conducted using the allelic, recessive, and dominant model, respectively.

Results: A total of 61 studies were included, reporting 120 environmental factors and 62 genetic variants. We found 12 risk factors (current overweight, overweight in adolescence, high waist circumference, smoking, alcohol, sugar beverages intake, sedentary behavior, red meat intake, family history of CRC, hypertension, hyperlipidemia and metabolic syndrome) and three protective factors (vitamin D, folate, and calcium intake) for EOCRC or EOCRA. No significant associations between the examined genetic variants and EOCRC risk were observed.

Conclusions: Current evidence indicates that changing patterns of traditional CRC risk factors may explain the rising incidence of EOCRC. However, research on novel risk factors for EOCRC is limited and therefore we cannot rule out the possibility of EOCR having different risk factors than older onset CRC.

Impact: The potential for the identified risk factors to enhance the identification of at-risk groups for personalized EOCRC screening and prevention and for the prediction of EOCRC risk should be comprehensively addressed by future studies.

Introduction

Colorectal cancer (CRC) is the third most common cancer in terms of incidence and the second leading cause of cancer-related death in the world[1]. Although the incidence of CRC in populations of all ages in many countries has remained stable or decreased largely due to increased and more effective CRC screening[2], the incidence of early-onset colorectal cancer (EOCRC) has been rising worldwide, which might be attributed to a birth cohort effect after 1950[3].

In general, EOCRC refers to cases diagnosed before the age of 50 and this cut-off is based on recommendations for CRC screening in high-income countries[4]. It has been suggested that EOCRC differs from late-onset colorectal cancer (LOCRC) in terms of several factors. For example, prior studies have shown that EOCRCs are more commonly left-sided and present with rectal bleeding and abdominal pain [5]. Furthermore, the histologic characteristics of EOCRC are more likely to be mucinous and signet-ring histology with reasons unknown[6]. Generally, EOCRC is more likely to be diagnosed at advanced stage and has poorer cell differentiation at diagnosis[7,8]. Even though the 5-year cancer-specific survival of EOCRC and LOCRC is somewhat comparable, EOCRC is associated with a higher risk of tumor metastasis and recurrence[6,9].

The etiology and reasons for the increasing incidence of EOCRC are unclear and are likely to be multifactorial, including interactions between genetic and environmental risk factors. For example, pathogenic germline variants have been demonstrated to be related to hereditary EOCRC risk[10]. Although hereditary syndromes play a crucial role in EOCRC risk[9,11], most cases are sporadic without identifiable cause and hereditary syndromes are unlikely to fully account for the increasing incidence of sporadic EOCRC[12]. In recent years, multiple studies have demonstrated strong associations between obesity in children, adolescents, or young adults and risk of sporadic EOCRC in several countries including Australia, USA, and Germany[13,14]. Other risk factors for EOCRC include unhealthy lifestyle factors such as unhealthy diet (e.g., high intake of processed meat, low fiber diet)[15], physical inactivity[16], and smoking[17].

Given the increasing incidence of CRC in younger adults in whom CRC screening is generally not recommended, synthesizing evidence on key risk factors for EOCRC may be relevant for enhanced tailored primary prevention and personalized screening for CRC in this population of special interest.

Some previous meta-analyses have partly addressed this knowledge gap[18,19], but they mostly focused on environmental risk factors or did not consider EOCRAs which are the precursors of most CRCs. In this study, we aim to search, appraise and synthesize available epidemiological evidence on the associations between environmental or genetic factors and risk of EOCRC and EOCRA.

Methods

The protocol for this study was registered in PROSPERO (registration number CRD42021269993), and the study was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Literature search and selection criteria

We conducted a comprehensive search in MEDLINE (1946-) and EMBASE (1974-) databases from inception to February 9, 2023. All identified publications went through a two-step parallel review (performed by R.Z. and N.Y.) based on predefined selection criteria. Further details of the specific search strategy and selection criteria can be found in **Supplementary Method**.

EOCRC was defined as CRC cases diagnosed before the age of 50 years[20]. EOCRA was defined as advanced colorectal adenomas diagnosed before the age of 50 years. Advanced adenomas included an adenoma ≥1 cm or adenoma with high-grade dysplasia or villous/tubulovillous histologic elements[21].

Data extraction

Data extraction was conducted independently by three investigators (R.Z., N.Y., and Y.Z.). All the extracted information was checked for accuracy by two other investigators (X.Z. and D.B.). The details of the data extraction strategy can be found in **Supplementary Method**.

Genotypic data of EOCRC from the UK Biobank

A list of genetic variants to be summarized using meta-analysis was generated from the included studies of the systematic review, which reported genetic associations with EOCRC. Additional genotypic data of these genetic variants from the UK biobank was incorporated to fully examine their associations using a nested case-control design and to more fully examine their relationship, we choose healthy population and LOCRC (CRC cases diagnosed older than 50 years old) as control groups, respectively. Details of the UK Biobank study and similar approaches to EOCRC analysis in the UK Biobank have been published previously[22,23].

Study quality assessment

We assessed the quality of case-control studies and cohort studies using the Newcastle-Ottawa Quality Assessment Scales. The National Institutes of Health (NIH) Quality Assessment Tool was used for cross-sectional studies. Two authors (N.Y. and R.Z.) rated the quality of the studies independently.

Statistical analysis

We conducted meta-analyses for environmental risk factors with at least two primary studies. For each risk factor, we estimated several metrics, including (i) the summary effect and 95% CIs using the random-effects model (DerSimonian Laird method), (ii) the heterogeneity among studies using the Q statistic and I^2 metric, (ii) the 95% prediction interval (PI), (iii) the presence of small study effects using the Egger's regression asymmetry test, and (iv) the excess significance test. For genetic variants, pooled ORs and 95% CIs were calculated for their associations with EOCRC compared to healthy controls and LOCRC patients respectively using allelic, recessive, and dominant genetic models. The Q statistic and I^2 metric were calculated to quantify heterogeneity. Funnel plot analysis with an Egger test was conducted to test for the small study effect. Statistical power was estimated by the Power and Sample Size Program[24]. Bayesian false-discovery probability (BFDP) was calculated to assess the credibility of the observed associations. All statistical analyses were performed using the "metafor" packages in R (version 4.0.2). For the studies that could not be included in the meta-analysis, we synthesized the evidence thematically and reported the results narratively.

Evidence credibility grading

The evidence credibility was assessed according to the criteria reported in **Supplementary Method**. Observational associations were categorized into four categories considering several metrics as described previously.[14] For genetic variants[24], we assessed the credibility of genetic association by using the BFDP[25] and the Venice criteria[26].

Data availability

Researchers can request the data we used from the UK Biobank (www.ukbiobank.ac.uk/).

Results

Study selection

Figure 1 shows the results of literature search. A total of 61 studies were included, of which 50 articles examined environmental risk factors and 11 articles investigated genetic risk factors. Of them, 44 articles provided enough data to perform meta-analyses. **Supplementary Table 1** shows the basic characteristics of the included studies, including 27 case-control studies, 25 cohort studies, and 9 cross-sectional studies. A total of 47 studies were on EOCRC, whereas 14 were on EOCRA. We classified the examined risk factors into six categories: sociodemographic factors (n=8), anthropometric factors (n=19), personal medical history or family history (n=34), medication use (n=11), lifestyle factors (n=28), and genetic factors (n=11). The details of the quality assessment are summarized in **Supplementary Table 2**.

Sociodemographic factors

We identified 11 studies investigating the association between sociodemographic factors and the risk of EOCRC or EOCRA. We defined high-level education as education up to college level or higher (with low-level education as the reference group) in the meta-analysis. Four studies and two studies examining the association between education level and risk of EOCRC and EOCRA, respectively, were included in the meta-analysis. The results of the meta-analysis demonstrated no significant association between education levels and the risk of EOCRC or EOCRA. A meta-analysis of three studies exploring the association between race or ethnicity and risk of EOCRC reported that Caucasian (pooled OR=1.59, 95% CI, 1.36-1.85) and African-American individuals (pooled OR=1.18, 95% CI, 1.04-1.35) had higher odds of EOCRC. (**Figures 2-3**). In a narrative synthesis of the studies that were not included in the meta-analysis, living with spouses and colonoscopy screening were associated with a lower risk of EOCRA. Asian and Hispanic individuals had a lower risk of EOCRA than White individuals. As for EOCRC, 1-2 times CT scan was associated with a lower risk of EOCRC while the occupation of farmers was associated with an increased risk of EOCRC. (**Supplementary Tables 3-4**).

Anthropometric factors

We identified 19 articles examining the relationship between anthropometric factors and EOCRC or EOCRA risk. Regarding EOCRC, the meta-analysis of 9 studies showed a positive but non-statistically significant association between current obesity and EOCRC (pooled OR=1.39, 95% CI, 0.99-1.94), while restricting the analysis to cohort studies showed a strong association (pooled OR=1.97, 95% CI, 1.38-2.83). Meta-analysis of three studies showed a 37% increased EOCRC risk among participants who were overweight in adolescence (pooled OR=1.37, 95% CI, 1.15-1.63) and the association was stable when restricting the analysis to cohort studies (pooled OR=1.41, 95%CI, 1.17-1.71). No significant association was found between obesity in adolescence and EOCRC risk while restricting the analysis to two cohort studies indicated a significant association (pooled OR=1.48, 95%CI, 1.11-1.96). High waist circumference was defined as ≥90cm for men and ≥80cm for women (normal circumference as the reference group) in our study. The result of meta-analysis bespeaks high waist circumference was associated with an increased risk of EOCRC (pooled OR=1.17, 95% CI, 1.01-1.34; **Figure 2**). A total of 6 articles explored the relationship between overweight and EOCRA and meta-analysis showed a positive association (pooled OR=1.33, 95% CI, 1.16-1.51) (**Figure 3**).

In the narrative synthesis of other studies, one prospective cohort study reported that weight gain of more than 40kg since age 18 (vs loss or gain <5.0kg) was associated with higher risk of EOCRC (RR=2.15; 95% CI, 1.01-4.55). By contrast, one retrospective cohort study showed that weight loss (vs stable weight) was associated with over seven-fold increased risk of EOCRC (OR=7.43, 95%CI 6.77-8.15). One nested case-control study suggested that waist-to-hip ratio of 0.73-0.78 (vs <0.72) was associated with lower risk of EOCRC (OR=0.45; 95%CI, 0.22-0.92). One cohort study investigated that body surface area (per m^2) was associated with EOCRC risk (RR=3.40; 95% CI, 3.30-3.50). **(Supplementary Table 3)**. Regarding EOCRA, one cross-sectional study showed a positive association between abdominal obesity and EOCRA risk (OR=1.28, 95%CI: 1.05-1.57) (**Supplementary Table 4**).

Personal medical or family history

We identified 34 studies examining the relationship between personal medical history or family history of CRC among first-degree relatives with EOCRC or EOCRA risk. In terms of EOCRC, 8

studies exploring the association between family history of CRC and EOCRC risk were included in the meta-analysis. Results showed a strong positive association between family history of CRC and EOCRC risk (pooled OR=5.81, 95% CI, 2.91-11.61). The association became stronger when restricting the analysis to cohort studies (three studies, pooled OR=6.64, 95%CI, 1.98-22.25). Meta-analysis of two studies showed a 51% increased EOCRC risk among participants with metabolic syndrome (two studies, pooled OR=1.51, 95% CI, 1.05-2.19) (**Figure 2)**. Regarding EOCRA, four risk factors were identified in meta-analyses: family history of CRC (seven studies, pooled OR=1.31, 95% CI, 1.14-1.50), hypertension (six studies, pooled OR=1.22, 95% CI, 1.05-1.41), hyperlipidemia (four studies, pooled OR=1.34, 95% CI, 1.01-1.79) and metabolic syndrome (three studies, pooled OR=1.37, 95% CI, 1.15-1.64). However, when restricting the analysis to cohort studies no significant association was found between family history of CRC and EOCRA risk. (**Figure 3**)

In a narrative synthesis of other studies, one retrospective study reported that abdominal pain (OR=4.73, 95%CI, 4.49-4.98), rectal pain (OR=7.48, 95%CI, 6.42-8.72), altered bowel function (OR=5.51, 95%CI, 5.19-5.85), rectal bleeding (OR=9.83, 95%CI, 9.12-10.60), and colitis (OR=4.10, 95%CI, 3.79-4.43) were positively associated with EOCRC risk. Furthermore, patients with iron deficiency anemia (HR=10.81, 95%CI, 8.15-14.33), hematochezia (HR=10.66, 95%CI, 8.76-12.97) and chronic kidney disease (HR=3.70, 95%CI, 1.83-7.49) were found had significantly higher risk of developing EOCRC. Another retrospective study reported that those with allergy or asthma (OR=0.62, 95%CI, 0.39-0.98), hyperthyroidism (OR=0.67, 95%CI, 0.48-0.94), and with higher parity (HR=10.81, 95%CI, 8.15-14.33) had lower risk of EOCRC **(Supplementary Table 3)**. Regarding EOCRA, pelvic irradiation (OR=12.8, 95%CI, 1.33-122) and anemia (OR=3.11, 95%CI, 1.32-7.34) were reported as risk factors, whereas previous use of screening sigmoidoscopy, colonoscopy, or barium enema (OR=0.26, 95%CI, 0.07-0.98) were associated with lower risk of EOCRA **(Supplementary Table 4)**.

Medication use

We identified 11 studies investigating the association between medication use and EOCRC or EOCRA risk. For EOCRC, it was demonstrated that ever use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) had inversely but non-statistically significant association with

EOCRC risk (pooled OR=0.89, 95% CI, 0.71-1.11) in the meta-analysis of three studies. On the contrary, the meta-analysis of three studies found a positive but non-statistically significant association between antibiotic use and EOCRC (pooled OR=1.17, 95% CI, 0.97-1.42). For EOCRA, no significant associations were found between the use of aspirin/NSAIDs (five studies, pooled OR=1.18, 95% CI, 0.90-1.55) or statin (two studies, pooled OR=1.20, 95% CI, 0.86-1.67) and risk of EOCRA **(Figure 2-3)**.

In a narrative synthesis of other studies, one retrospective study reported that tetracyclines use (OR=1.15, 95%CI, 1.02-1.29) and quinolones use (OR=1.52, 95%CI, 1.29-1.78) were positively associated with EOCRC risk (**Supplementary Tables 3**).

Lifestyle factors

A total of 28 studies explored the association between lifestyle factors (i.e., cigarette smoking, alcohol consumption, dietary supplement use, physical activity) and EOCRC or EOCRA risk.

In our meta-analyses of all studies combined, cigarette smoking (seven studies, pooled OR=1.62, 95% CI, 1.26-2.07), alcohol consumption (six studies, pooled OR=1.49, 95% CI, 1.28-1.74), sedentary lifestyle (three studies, pooled OR=1.42, 95% CI, 1.00-2.01), sugar beverages intake (two studies, pooled OR=2.58, 95% CI, 1.61-4.13) and red meat intake (three studies, pooled OR=1.12, 95% CI, 1.07-1.17) were significantly associated with EOCRC risk. The association with smoking became stronger when the analysis was restricted to cohort studies (three studies, pooled OR=2.34, 95% CI, 1.99-2.76). By contrast, vitamin D intake (three studies, pooled OR=0.70, 95% CI, 0.59-0.95), folate intake (three studies, pooled OR=0.77, 95% CI, 0.60-0.99) and calcium intake (three studies, pooled OR=0.82, 95% CI, 0.68-1.00) were inversely associated with EOCRC risk. The association with fruits and vegetables was based on three studies, all using the FFQ questionnaire to assess fruit and vegetable intake. Even though fruit and vegetable intake were inversely associated with EOCRC risk, the associations were not statistically significant **(Figure 2)**. Concerning EOCRA, smoking (six studies, pooled OR=1.56, 95% CI, 1.27-1.92) was associated with an increased risk of EOCRA and the association was stronger when the analysis was restricted to cohort studies (two studies, pooled OR=2.38, 95% CI, 1.41-4.02) **(Figure 3).**

In a narrative synthesis of the studies that were not included in the meta-analysis, a significantly higher risk of EOCRC or EOCRA was associated with a high westernized dietary pattern score, high sulfur microbial diet score, and western dietary pattern. In contrast, β-carotene supplements, vitamin C supplements, vitamin E supplements, prudent dietary pattern, dietary approaches to stopping hypertension (DASH), alternative Mediterranean dietary pattern, alternative healthy eating index-2010 (AHEI-2010) and Chinese food pagoda (CHFP) were all associated with reduced risk of EOCRC or EOCRA. On the contrary, higher sulfur microbial diet score and western dietary pattern were associated with increased risk of EOCRC or EOCRA. (**Supplementary Table 3-4**).

Genetic factors

A total of 11 studies explored the associations between 62 genetic variants and EOCRC risk **(Supplementary Table 5)**. Using genetic data from the UK Biobank, we examined the associations between these reported genetic variants and EOCRC risk (N_{case}= 618) in three genetic models **(Supplementary Table 6-7)**. Of them, only two variants rs4939827 (located within *SMAD7,* OR=0.78, 95% CI:0.69-0.89, P=1.59×10^{-4}) and rs961253 (intergenic variant, OR=1.24, 95% CI:1.09-1.41, P=9.45×10^{-4}) showed nominally significant associations with EOCRC in the allelic model. When meta-analysis was conducted to synthesize data from published studies and those from the UK Biobank, no statistically significant associations with EOCRC risk were observed in any of the three genetic models after correction for multiple testing. The summary crude ORs and 95% CI for the allelic, dominant, and recessive models are presented in **Table 1**.

Evidence grading

We applied our evidence classification criteria to grade the level of evidence from the included studies (**Figure 2-3**). Based on the metrics of evidence grading, no environmental factor presented convincing evidence; six factors for EOCRC and four factors for EOCRA presented highly suggestive evidence. The remaining eight and two statistically significant factors presented weak evidence for EOCRC and EOCRA, respectively. For genetic factors, none of the associations had suggestive evidence and all of them were “non-significant”. The detailed summary statistics of highly suggestive risk factors for EOCRC and EOCRA are depicted in **Figures 4** and **5**.

Discussion

In this study, we conducted a systematic review and meta-analysis of observational studies to comprehensively assess the role of genetic and environmental factors in EOCRC and EOCRA risk. A total of 120 environmental factors and 62 genetic factors were thoroughly investigated in this study. Our meta-analysis demonstrated that 12 factors (current overweight, overweight in adolescence, high waist circumference, smoking, alcohol, sugar beverages intake, sedentary behavior, red meat intake, family history of CRC, hypertension, hyperlipidemia, and metabolic syndrome) were associated with increased risk of EOCRC or EOCRA. By contrast, intake of calcium, folate, and vitamin D was associated with a reduced risk of EOCRC. Current evidence suggests that the risk factors of EOCRC are similar to those for CRC in the general population. Nevertheless, because of limited research specific risk factors of EOCRC might have not been identified yet. Future studies should determine whether changing patterns of traditional risk factors or increasing prevalence of other risk factors are contributing to the apparent rising incidence of EOCRC.

In our study, Caucasian and African-American individuals had higher odds of EOCRC, while Asian and Hispanic individuals had a lower risk of EOCRA than White individuals. This finding is generally consistent with a population-based study [27] of elderly Medicare enrollees which reported the interval CRC risk was 31% higher in Blacks compared to Whites while was lower among Asians. Given the limited study evidence, future efforts should be made to explore the racial and ethnic disparities in EOCRC incidence.

Family history of CRC in at least one first-degree relative is an established risk factor for CRC in the general population[28] and our meta-analysis indicated that family history of CRC is also a strong risk factor for both EOCRC and EOCRA. The association could be related to the high prevalence of the mutation in the high-penetrance cancer-susceptibility genes. Given this, the National Comprehensive Cancer Network recommends genetic risk counseling and evaluation for EOCRC patients[12]. Individuals with family history of CRC are regarded as high-risk and it is recommended that they undergo colonoscopy screening more frequently or at an earlier age than the general population[29]. Metabolic syndrome was identified as a risk factor for EOCRC in our meta-analysis,

but only a few studies were included in this analysis. Aspirin has been shown in previous studies to have the potential for the chemoprevention of CRC, and our study also demonstrated that its use is inversely associated with EOCRC risk[30]. A previous RCT study has shown that regular use of aspirin at or after age 70 years is associated with a lower risk of CRC[31]. Given that the evidence regarding the inverse association with CRC risk has mostly been examined in the general population, further studies focusing on populations younger than 50 years are required for a more comprehensive conclusion on the potential for aspirin to reduce EOCRC risk. Oral antibiotic is known to impact the gut microbiome and long-term use is probably a risk factor not only for CRC but also for colorectal adenomas[32,33]. Even though there are limited studies on its impact, oral antibiotics may confer an impetus on EOCRC risk. Further studies are needed to confirm this link.

Regarding lifestyle factors, compared with non-drinkers, alcohol drinking was identified as a common risk factor for both EOCRC and EOCRA in our meta-analysis. A previous study has found that alcohol consumption is associated with CRC risk in patients of all ages [34]. Despite a lack of large studies and rigorous research, alcohol consumption is suspected to be associated with EOCRC risk[20]. In one previous systematic review and meta-analysis, Sullivan et al.[18] also found alcohol as a risk factor for EOCRC. With the increasing alcohol consumption in many countries[35], future studies should assess the exact dose-response relationship between alcohol use and EOCRC/EOCRA risk.

Our study also demonstrated associations between sedentary behavior and EOCRC risk. The presence of a sedentary lifestyle was mostly defined as having any type of physical activity less than 1 hour per week[36]. Sedentary behavior may result in energy imbalance[37] and progressively lead to being overweight or obese, a factor that was found to be associated with increased EOCRC/EOCRA risk in our study. Aside from obesity/overweight and sedentary behavior, high waist circumference was also identified as a risk factor for EOCRC in this meta-analysis. In a previous meta-analysis of six observational studies by Li et al[19], obesity was also found to be associated with approximately 90% increased risk of EOCRC. The prevalence of obesity in the USA and many developed countries is increasing, especially among adolescents and young adults[38]. The rising trend of obesity prevalence corresponds to the increased trend of EOCRC incidence. As an established risk factor for CRC in populations of all ages, the rising obesity rates among young

adults and adolescents may play an important role in increased EOCRC risk. In our study, being overweight in adolescence was also a risk factor for EOCRC. Liu et al.[39] conducted a cohort study exploring the association between weight change in adolescence and EOCRC and found that each 5-kg weight increase contributed to a 9% increased risk of EOCRC. A case-control study[23] explored that having a higher weight or height than peers at age of 10 could positively impact the risk of EOCRC. These discoveries suggest that early life exposures including being overweight among adolescents might be an emerging risk factor for EOCRC, however, the available data from included studies are insufficient. Future studies could focus on investigating the association between early life exposure and EOCRC/EOCRA risk.

In our study, smoking was associated with an increased risk of EOCRC and EOCRA. Multiple studies have reported smoking as a risk factor for CRC among the general population[40]. However, the prevalence of smoking is decreasing in many countries with the incidence of EOCRC rising[41]. Furthermore, there remains debate about the impact of different times since starting smoking on the risk of CRC. Micronutrients such as calcium, vitamin D, and folate intake were inversely associated with EOCRC risk in our meta-analysis. This finding warrants further investigation to identify potential mechanisms explaining this association. Red meat intake and sugar beverages intake were considered risk factors for EOCRC in our study. Higher red or processed meat intake has been regarded as a risk factor for CRC in the general population[42,43]. Potential mechanisms explaining the associations between red and processed meat intake and CRC risk include gut epithelial damage and proliferation, DNA damage, and genotoxicity[44]. Whether these mechanisms also hold for EOCRC is unclear and warrants further investigations. Previous studies[45,46] have reported that sugar-sweetened beverage (SSB) consumption was related to the incidence of CRC in general which was consistent with our finding. While studies exploring the potential mechanisms of this association are still needed.

A major strength of our meta-analysis was the consideration of genetic factors and their associations with EOCRC risk. Two genetic variants (rs4939827 and rs961253) showed nominally significant associations with EOCRC in the allelic model using data from UK Biobank. Even though genetic polymorphisms alone may not necessarily indicate the presence of or susceptibility to CRC or colorectal adenoma, the presence of these and other risk factors of CRC (e.g., alcohol consumption,

physical inactivity, and overweight) may require further clinical assessment and interventions, as a combination of these factors may have an additive and/or multiplicative effect on the risk of CRC in both the general population and younger adults [47,48].

The starting age of CRC screening in most countries is more than 50 years old. The starting age of CRC screening in most countries is more than 50 years old. The 2021 American College of Gastroenterology CRC screening guidelines[49] suggested that CRC screening should be conducted in average-risk individuals between ages 45 and 49 years. A recent study[50] also showed that starting CRC screening at the age of 45 years is likely to be cost-effective and a greater benefit could be achieved by increasing participation rates for higher-risk individuals. However, it may impractical or even not feasible to extend CRC screening to all young adults because of the risk of morbidity and very low risk of mortality as well as the financial costs of colonoscopy, evaluating the key risk factors for EOCRC may be useful for identifying high-risk groups to lower the cost of screening. The modifiable risk factors identified in our study could be useful for personalized CRC screening and prevention in adolescents and younger adults. Meanwhile, it is essential to construct risk-scoring algorithms which incorporate these important risk factors. A risk assessment system might enhance the prediction and risk stratification for EOCRC and contribute to primary prevention strategies. In addition, CRC screening based on risk stratification instead of age-based screening, may allow adults to benefit more[51].

Our study has several strengths. To our knowledge, this field synopsis is the first to investigate both genetic and environmental risk factors of CRC in populations under the age of 50. Our study thus makes an important contribution to the limited evidence on risk factors for EOCRC, a topic that has gained much attention in the last few years. We searched multiple databases, and study selection and data extraction were done by multiple authors, minimizing the risk of study selection bias and data extraction errors. Our study also has limitations. First, there were a limited number of studies meeting our inclusion criteria and we included some articles that used differing definitions of both EOCRC and risk factors, which might contribute to the observed between-study heterogeneity in some of the associations. The limited number of studies precluded us from conducting a meta-regression analysis to rule out sources of heterogeneity. Second, different covariates were adjusted for in the included studies. Thus, the results of our meta-analysis may be affected by residual

confounding due to unmeasured or less accurately measured factors. Lastly, publication bias (e.g., location bias, language bias, or selective outcome reporting) is a general weakness of almost all meta-analyses including this study.

Current evidence did not identify the bespoke risk factor of EOCRC yet because of limited research. Future studies should determine whether changing patterns of traditional risk factors or increasing prevalence of other risk factors (e.g., microbiome and early life exposure) are contributing to the apparent rising incidence of EOCRC. The potential for identifying risk factors to enhance the identification of at-risk groups for personalized EOCRC screening and prevention and for prediction of EOCRC risk aside from the family history of CRC should be comprehensively addressed by future studies.

Table1 Pooled effect estimates and 95% confidence intervals (95% CI) between early-onset colorectal cancer (EOCRC) and genetic risk factors

SNP	Cases/ Controls	Gene	Ref. allele	Risk allele	No. of studies	Allelic model: per allele						Recessive model: var/var vs wt/wt and wt/var						Dominant model: wt/var and var/var vs wt/wt					
						Effect size		Heterogeneity		Credibility		Effect size		Heterogeneity		Credibility		Effect size		Heterogeneity		Credibility	
						OR (95%CI)	*P* value	I^2(%)	Power	Venice criteria grade*	BFDP**	OR (95% CI)	*P* value	I^2 (%)	Power	Venice criteria grade*	BFDP**	OR (95% CI)	*P* value	I^2 (%)	Power	Venice criteria grade*	BFDP**
EOCRC vs Late-onset colorectal cancer																							
rs10411210	1245/ 11380	*RHPN2*	C	T	3	1.09 (0.96, 1.25)	0.189	0.00	0.160	CAB	0.954	1.03 (0.64, 1.67)	0.897	0.00	0.054	CAB	0.965	0.89 (0.77, 1.03)	0.129	0.00	0.329	CAB	0.949
rs10505477	1054/ 10119	*CASC8*	A	G	2	1.09 (0.96, 1.24)	0.197	46.12	0.255	CBB	0.952	0.89 (0.76, 1.04)	0.150	0.63	0.299	CCB	0.948	0.90 (0.75, 1.08)	0.230	30.58	0.307	CBB	0.949
rs10774214	1054/ 10119	*CCND2-AS1*	T	C	2	1.05 (0.96, 1.16)	0.281	0.00	0.111	CAB	0.961	0.94 (0.82, 1.08)	0.368	0.00	0.142	CAB	0.952	0.93 (0.78, 1.10)	0.383	0.00	0.142	CAB	0.952
rs10795668	1245/ 11380	*LOC105376400*	G	A	3	0.98 (0.87, 1.10)	0.708	37.66	0.058	CBB	0.960	**1.23 (1.02, 1.48)**	**0.031**	**0.00**	0.515	BAB	0.862	0.95 (0.77, 1.17)	0.645	60.98	0.074	CCB	0.958
rs10849432	1054/ 10119	Intergenic	C	T	2	1.04 (0.91, 1.20)	0.569	0.00	0.067	CAB	0.966	0.95 (0.82, 1.11)	0.533	0.00	0.106	CAB	0.955	0.94 (0.56, 1.58)	0.801	0.00	0.069	CAB	0.962
rs10936599	1054/ 10119	*MYNN*	C	T	2	0.97 (0.88, 1.08)	0.603	0.00	0.069	CAB	0.957	1.07 (0.89, 1.29)	0.475	0.00	0.113	CAB	0.965	1.01 (0.88, 1.17)	0.852	0.00	0.052	CAB	0.965
rs11169552	1054/ 10119	*ATF1, LOC105369765*	C	T	2	0.98 (0.88, 1.08)	0.671	0.00	0.058	CAB	0.959	1.09 (0.86, 1.37)	0.486	0.00	0.119	CAB	0.964	1.01 (0.88, 1.15)	0.906	0.00	0.053	CAB	0.965
rs11196172	1054/ 10119	*TCF7L2*	G	A	2	0.96 (0.85, 1.08)	0.498	0.00	0.074	CAB	0.955	0.98 (0.80, 1.20)	0.830	0.00	0.054	CAB	0.962	1.11 (0.93, 1.32)	0.242	0.00	0.224	CAB	0.956
rs12603526	1054/ 10119	Intergenic	T	C	2	1.02 (0.88, 1.18)	0.816	0.00	0.055	CAB	0.966	0.95 (0.69, 1.31)	0.743	0.00	0.059	CAB	0.961	0.99 (0.82, 1.19)	0.924	0.00	0.051	CAB	0.963
rs1535	1054/ 10119	*FADS2*	A	G	2	0.97 (0.88, 1.08)	0.581	6.23	0.071	CAB	0.969	1.03 (0.84, 1.26)	0.806	25.59	0.065	CBB	0.966	1.04 (0.89, 1.21)	0.534	0.00	0.080	CAB	0.966
rs1665650	1054/ 10119	*HSPA12A*	T	C	2	1.04 (0.94, 1.16)	0.393	0.00	0.083	CAB	0.965	0.96 (0.84, 1.09)	0.534	0.00	0.094	CAB	0.956	0.90 (0.72, 1.14)	0.385	0.00	0.178	CAB	0.952
rs16892766	809 / 9854	*EIF3H*	A	C	2	0.94 (0.78, 1.12)	0.464	0.00	0.070	CAB	0.955	0.84 (0.36, 1.92)	0.669	0.00	0.054	CAB	0.959	1.09 (0.90, 1.32)	0.370	0.00	0.182	CAB	0.963
rs174537	1054/ 10119	*MYRF*	G	T	2	1.03 (0.93, 1.14)	0.595	0.00	0.071	CAB	0.966	0.93 (0.75, 1.16)	0.536	0.00	0.093	CAB	0.955	0.98 (0.86, 1.12)	0.742	0.00	0.061	CAB	0.961
rs174550	1054/ 10119	*FADS1*	T	C	2	0.97 (0.87, 1.08)	0.599	9.80	0.071	CAB	0.957	1.04 (0.88, 1.24)	0.631	5.35	0.077	CAB	0.966	1.03 (0.88, 1.20)	0.739	0.00	0.067	CAB	0.966
rs1800469	1054/ 10119	*B9D2, TGFB1*	A	G	2	1.09 (0.99, 1.20)	0.091	0.00	0.229	CAB	0.924	0.88 (0.77, 1.01)	0.061	0.00	0.456	CAB	0.950	0.95 (0.78, 1.15)	0.571	0.00	0.089	CAB	0.957
rs1957636	1054/ 10119	*LOC105370507*	T	C	2	1.02 (0.93, 1.12)	0.646	0.00	0.060	CAB	0.966	0.98 (0.85, 1.14)	0.801	0.00	0.058	CAB	0.961	0.96 (0.82, 1.12)	0.573	0.00	0.085	CAB	0.957
rs2241714	1054/ 10119	*B9D2, TMEM91*	T	C	2	1.09 (0.99, 1.20)	0.086	0.00	0.229	CAB	0.924	0.88 (0.77, 1.01)	0.073	0.00	0.456	CAB	0.950	0.93 (0.77, 1.13)	0.454	0.00	0.128	CAB	0.954
rs2423279	1054/ 10119	Intergenic	T	C	2	0.94 (0.85, 1.05)	0.265	0.00	0.124	CAB	0.950	1.04 (0.80, 1.35)	0.771	0.00	0.063	CAB	0.966	1.09 (0.95, 1.24)	0.208	0.00	0.255	CAB	0.952
rs3802842	1054/ 10119	*COLCA1, COLCA2*	C	A	3	1.02 (0.85, 1.21)	0.864	69.53	0.061	CCB	0.966	0.94 (0.71, 1.25)	0.675	78.72	0.149	CCB	0.959	1.08 (0.89, 1.31)	0.421	0.00	0.129	CAB	0.964
rs4246215	1054/ 10119	*FEN1*	G	T	2	1.05 (0.95, 1.16)	0.349	0.00	0.109	CAB	0.961	0.94 (0.76, 1.17)	0.580	0.00	0.083	CAB	0.957	0.94 (0.83, 1.07)	0.373	0.00	0.155	CAB	0.951
rs4444235	1245/ 11380	Intergenic	T	C	3	1.01 (0.92, 1.10)	0.866	0.00	0.053	CAB	0.966	0.97 (0.85, 1.12)	0.704	0.00	0.067	CAB	0.959	1.01 (0.88, 1.16)	0.911	0.00	0.052	CAB	0.965
rs4779584	627/ 2790	GREM1	C	T	2	0.90 (0.72, 1.14)	0.386	48.35	0.221	CBB	0.965	0.76 (0.57, 1.01)	0.062	0.00	0.450	CAB	0.945	1.00 (0.80, 1.26)	0.989	0.00	0.050	CAB	0.954
rs4813802	1054/ 10119	Intergenic	T	G	2	0.97 (0.85, 1.10)	0.602	33.69	0.069	CBB	0.958	1.08 (0.88, 1.34)	0.449	0.00	0.118	CAB	0.965	1.02 (0.85, 1.22)	0.841	43.76	0.060	CBB	0.966
rs4925386	1054/ 10119	*LAMA5*	T	C	2	1.03 (0.90, 1.17)	0.677	34.24	0.067	CBB	0.966	0.96 (0.84, 1.10)	0.568	5.17	0.094	CAB	0.956	1.02 (0.79, 1.31)	0.901	0.00	0.052	CAB	0.965
rs4939827	809/ 9854	*SMAD7*	T	C	2	1.04 (0.94, 1.16)	0.455	0.00	0.083	CAB	0.965	0.96 (0.79, 1.16)	0.662	0.00	0.068	CAB	0.959	0.94 (0.81, 1.10)	0.455	0.00	0.129	CAB	0.954
rs647161	1054/ 10119	*C5orf66*	C	A	2	1.03 (0.92, 1.14)	0.653	18.28	0.071	CAB	0.966	0.98 (0.85, 1.14)	0.818	0.00	0.058	CAB	0.961	0.93 (0.71, 1.22)	0.594	62.17	0.149	CCB	0.957
rs6687758	1054/ 10119	Intergenic	A	G	2	1.10 (0.99, 1.23)	0.078	0.00	0.245	CAB	0.931	0.87 (0.65, 1.16)	0.338	0.00	0.148	CAB	0.951	0.89 (0.78, 1.02)	0.092	0.00	0.401	CAB	0.949
rs6983267	1245/ 11380	*CASC8, CCAT2*	G	T	3	1.02 (0.94, 1.12)	0.559	0.00	0.052	CAB	0.964	0.96 (0.83, 1.11)	0.804	0.00	0.084	CAB	0.954	0.98 (0.85, 1.12)	0.768	0.00	0.072	CAB	0.965
rs7014346	1054/ 10119	*CASC8*	A	G	2	1.01 (0.89, 1.15)	0.874	40.98	0.052	CBB	0.965	0.97 (0.85, 1.11)	0.666	0.00	0.072	CAB	0.959	1.03 (0.81, 1.31)	0.814	32.87	0.060	CBB	0.966
rs704017	1054/ 10119	*ZMIZ1-AS1*	A	G	2	1.15 (0.90, 1.47)	0.276	83.42	0.542	BCB	0.958	0.84 (0.56, 1.25)	0.389	75.91	0.590	BCB	0.952	0.82 (0.63, 1.07)	0.148	66.50	0.760	BCB	0.948
rs7136702	1054/ 10119	Intergenic	T	C	2	0.98 (0.88, 1.08)	0.658	14.77	0.061	CAB	0.959	1.02 (0.88, 1.17)	0.822	0.00	0.059	CAB	0.966	1.06 (0.85, 1.33)	0.593	36.67	0.102	CBB	0.966
rs7229639	1054/ 10119	*SMAD7*	A	G	2	0.98 (0.85, 1.12)	0.713	0.00	0.057	CAB	0.961	1.03 (0.88, 1.20)	0.714	0.00	0.067	CAB	0.966	1.03 (0.67, 1.59)	0.894	0.00	0.051	CAB	0.965
rs7758229	1054/ 10119	*SLC22A3*	G	T	2	1.02 (0.92, 1.13)	0.653	0.00	0.059	CAB	0.966	1.12 (0.90, 1.40)	0.293	0.00	0.185	CAB	0.961	0.92 (0.81, 1.05)	0.227	0.00	0.238	CAB	0.949
rs961253	1245/ 11380	Intergenic	C	A	3	0.99 (0.86, 1.15)	0.927	41.51	0.052	CCB	0.965	0.96 (0.66, 1.41)	0.851	43.95	0.083	CBB	0.962	1.03 (0.91, 1.18)	0.614	0.00	0.058	CAB	0.965
rs9929218	1245/ 11380	*CDH1*	G	A	3	1.09 (0.98, 1.21)	0.106	0.00	0.233	CAB	0.935	0.82 (0.63, 1.08)	0.157	0.00	0.255	CAB	0.948	0.93 (0.82, 1.05)	0.232	0.00	0.209	CAB	0.949
EOCRC vs Healthy controls																							
rs755622	668/ 3232	*MIF*	G	C	2	0.75 (0.45, 1.27)	0.287	71.85	0.683	BCB	0.952	2.42 (0.40, 14.66)	0.335	63.02	0.990	ACB	0.964	1.30 (0.76, 2.22)	0.338	63.08	0.844	ACB	0.963
rs4073	664/ 3244	*IL-8*	A	T	2	1.24 (0.75, 2.05)	0.402	77.74	0.707	BCB	0.963	0.86 (0.51, 1.46)	0.586	40.86	0.327	CBB	0.957	0.44 (0.08, 2.45)	0.352	90.56	1.000	ACB	0.951
rs1800629	664/ 3244	*TNF-α*	G	A	2	0.90 (0.75, 1.07)	0.230	7.45	0.150	CAB	0.949	1.31 (0.85, 2.01)	0.217	0.00	0.257	CAB	0.954	1.17 (0.83, 1.64)	0.377	31.44	0.428	CBB	0.962
rs5498	664/ 3244	*ICAM-1*	A	G	2	0.92 (0.73, 1.16)	0.489	28.09	0.155	CBB	0.955	1.09 (0.87, 1.37)	0.458	0.00	0.121	CAB	0.964	1.18 (0.73, 1.91)	0.495	55.73	0.452	CCB	0.965
rs13181	768/ 3240	*XPD*	T	G	2	\	\	\	\	\	\	\	\	\	\	\	\	1.67 (0.50, 5.58)	0.405	90.64	1.000	ACB	0.963
rs1799782	666/ 3138	*XRCC1*	G	A	2	\	\	\	\	\	\	\	\	\	\	\	\	3.51 (0.41, 29.94)	0.252	88.11	1.000	ACB	0.957

*Venice criteria including three specific criteria: the volume of evidence, the extent of replication and protection from bias. Statistical power was used to assess the volume of evidence, we used Power and Sample Size Program to estimate statistical power: A,＞80%; B, 50-79%; C,＜50%. The extent of replication was assessed by I^2 value: A, ＜25%; B, 25-49%; C,＞50%. The protection from bias was assessed by Egger test: B, no small study effect was detected; C, small study effect.

**Bayesian False Discovery Probability (BFDP) value was calculated at prior probability of 0.05. BFDP level of noteworthiness is 0.2.

Table and Figure legends

Table1 Pooled effect estimates and 95% confidence intervals (95% CI) between early-onset colorectal cancer and genetic risk factors. *Venice criteria including three specific criteria: the volume of evidence, the extent of replication and protection from bias. Statistical power was used to assess the volume of evidence, we used Power and Sample Size Program to estimate statistical power: A,＞80%; B, 50-79%; C,＜50%. The extent of replication was assessed by I^2 value: A, ＜ 25%; B, 25-49%; C,＞50%. The protection from bias was assessed by Egger test: B, no small study effect was detected; C, small study effect. **Bayesian False Discovery Probability (BFDP) value was calculated at prior probability of 0.05. BFDP level of noteworthiness is 0.2.

Figure 1 Flow chart for the search and selection of eligible studies.

Figure 2 Pooled effect estimates and 95% confidence interval (95%CI) between early-onset colorectal cancer and environmental risk factors. 1. NS=non-significant; OR=odds ratio; CI=confidence interval; PI=prediction interval. 2. Evidence grade criteria: Convincing (class I): statistical significance with $P<1\times10^{-6}$; included more than 1000 cases; I^2 <50%; 95% prediction intervals excluding the null value; no evidence of small study effects (P > 0.10) and of excess significance bias (P > 0.10). Highly suggestive (class II): statistical significance with $P < 1\times10^{-3}$; included more than 1000 cases; the largest component study reporting a significant result (P<0.05). Suggestive (class III): statistical significance with P < 0.01; included more than 1000 cases. Weak (class IV): statistical significance with P < 0.05. Non-significant: P > 0.05.

Figure 3 Pooled effect estimates and 95% confidence interval (95%CI) between early-onset advanced colorectal adenomas and environmental risk factors. 1. NS=non-significant; OR=odds ratio; CI=confidence interval; PI=prediction interval. 2. Evidence grade criteria: Convincing (class I): statistical significance with $P<1\times10^{-6}$; included more than 1000 cases; I^2 <50%; 95% prediction intervals excluding the null value; no evidence of small study effects (P > 0.10) and of excess significance bias (P > 0.10). Highly suggestive (class II): statistical significance with $P < 1\times10^{-3}$; included more than 1000 cases; the largest component study reporting a significant result (P<0.05). Suggestive (class III): statistical significance with P < 0.01; included more than 1000 cases. Weak (class IV): statistical significance with P < 0.05. Non-significant: P > 0.05.

Figure 4 The summary statistics of highly suggestive risk factors for EOCRC

Figure 5 The summary statistics of highly suggestive risk factors for EOCRA

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