SYSTEMATIC REVIEWS AND META-ANALYSES

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Risk Factors for Early-Onset Colorectal Cancer: A Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit on page e1500. Upon completion of this activity, successful learners will be able to, 1) Identify potential risk factors for early-onset colorectal cancer; and, 2) Explain the importance of establishing risk factors for this unique patient population.

BACKGROUND & AIMS: **Despite the widespread increase in the incidence of early-onset colorectal cancer (EoCRC), the reasons for this increase remain unclear. The objective of this study was to determine risk factors for the development of EoCRC.**

METHODS: **We conducted a systematic literature review and meta-analysis of studies examining non-genetic risk factors for EoCRC, including demographic factors, comorbidities, and lifestyle factors. Random effects meta-analyses were conducted for risk factors that were examined in at least three studies. Heterogeneity was investigated using the Q-test and I^2 statistic.**

RESULTS: **From 3304 initial citations, 20 studies were included in this review. Significant risk factors for EoCRC included CRC history in a first-degree relative (RR 4.21, 95% CI 2.61-6.79), hyperlipidemia (RR 1.62, 95% CI 1.22-2.13), obesity (RR 1.54, 95% CI 1.01-2.35), and alcohol consumption (high vs. non-drinkers) (RR 1.71, 95% CI 1.62-1.80). While smoking was suggestive as a risk factor, the association was not statistically significant (RR 1.35, 95% CI 0.81-2.25). With the exception of alcohol consumption, there was considerable heterogeneity among studies (I^2 > 60%). Other potential risk factors included hypertension, metabolic syndrome, ulcerative colitis, chronic kidney disease, dietary factors, sedentary behaviour, and occupational exposure to organic dusts, but these were only examined in one or two studies.**

CONCLUSIONS: **The results of this study advance the understanding of the etiology of EoCRC. High-quality studies conducted on generalizable populations and that comprehensively examine risk factors for EoCRC are required to inform primary and secondary prevention strategies.**

Keywords: Colorectal Cancer; Early-Onset; Risk Factors; Lifestyle Factors; Demographics; Comorbidities.

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related death.[1] Although the risk of CRC increases with age, approximately 10% of newly diagnosed cases occur in adults younger than the age of 50, termed *early-onset colorectal cancer* (EoCRC).[2] Furthermore, despite a decrease in the incidence of CRC among older age groups,[3,4] an increase in the incidence of EoCRC has been observed in recent decades in Canada,[3] the United States,[4] and in several other countries including Australia, Brazil, China, Japan, and the United Kingdom.[5] A systematic review of all studies examining population-level trends in the incidence of EoCRC reported similar findings.[6]

The reasons for these increasing trends in EoCRC are unclear. Although similar in magnitude between men and women,[6] some evidence suggests that the increases have been more pronounced among Caucasians.[7] In addition, the heterogeneity in the rise in cases and the variable tumor sites involved in the colorectum between

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; EoCRC, early-onset colorectal cancer; NOS, Newcastle-Ottawa Scale; RR, relative risk.**

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countries provide support for environmental and lifestyle factors to be potential contributors.[5] Because of the widespread nature of this increasing health problem and the magnitude of loss to young people when diagnosed with these more aggressive cancers,[8] these unfavorable changes in the epidemiology of EoCRC is a global concern and an important topic of investigation.

The majority of EoCRC cases are diagnosed outside of CRC screening programs. As such, these cancers are typically diagnosed at later stages, where prognosis is worse compared with CRCs diagnosed earlier.[8] EoCRC tumors commonly have poorer cell differentiation and a higher prevalence of signet ring cell histology and are more often located in the left side of the colon when compared with older-onset CRC.[8] Although 30% of EoCRC occurs among those with a family history of CRC or a genetic predisposition, the majority of cases are sporadic and possibly exacerbated by environmental or lifestyle factors.[9]

Establishing risk factors for EoCRC is an important exercise, because it can inform both primary prevention efforts aimed at behavior modification and secondary prevention strategies such as targeted screening approaches for high-risk individuals. Several review articles on EoCRC have been published and have qualitatively summarized the evidence on potential risk factors for EoCRC.[8,10,11] To our knowledge, there has only been one study that has quantitatively summarized risk factors for EoCRC with a meta-analysis. In their review, Breau and Ellis[12] examined the association of clinical and lifestyle factors with the development of early-onset colorectal adenomas and cancer together. Because many colorectal adenomas do not develop into CRC, it is important to determine risk factors for EoCRC alone. In addition, there have been several articles that have examined risk factors for EoCRC that have been published recently. Therefore, the objective of this study was to determine risk factors for EoCRC and to quantify the magnitude of risk associated with these risk factors through a quantitative synthesis of the evidence base. In addition to summarizing the literature, this review sought to highlight gaps in knowledge that can be targeted for future research investigations on risk factors for EoCRC.

What You Need to Know

Background

Despite the widespread increase in the incidence of early-onset colorectal cancer (EoCRC), the reasons for this increase remain unclear.

Findings

Significant risk factors for EoCRC include colorectal cancer history in a first-degree relative, obesity, hyperlipidemia and alcohol consumption, while smoking is a suggestive risk factor.

Implications for patient care

The results of this study can inform primary prevention programs and targeted screening to reduce the incidence of EoCRC and associated mortality.

Methods

Literature Search, Eligibility Criteria, and Screening

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42020185557) and was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses[13] and Meta-analysis of Observational Studies in Epidemiology recommendations.[14] We systematically searched MEDLINE and Embase databases from inception to August 5, 2020 with a search strategy that was developed by D.E.O and R.L.S. in collaboration with a research librarian at the University of Calgary. The full search strategy is provided in the Supplementary Material. Abstract and title screening was conducted by S.T., K.C., and J.F. Any conflicts were resolved by D.E.O. Full-text screening was performed by D.E.O and R.L.S, and any conflicts were resolved by consensus.

To be eligible for inclusion, studies had to report findings from an observational study that examined the relationship of non-genetic factors that may increase the risk of developing EoCRC, defined as CRC diagnosed before the age of 50. Eligible risk factors included lifestyle or environmental factors, reproductive factors, comorbidities, or demographic characteristics. Any prospective or retrospective cohort studies, case-control studies, or cross-sectional studies were eligible for inclusion. During full-text screening, only published studies that compared risk factors between EoCRC cases and healthy individuals younger than the age of 50 were eligible for inclusion. Studies were excluded if they (1) only examined risk factors for advanced polyps or combined advanced polyps with CRC in the outcome definition, (2) compared characteristics between EoCRC cases and older-onset cases, (3) compared incidence rates of EoCRC for a specific cohort with standardized incidence rates in the general population, (4) did not report an effect estimate or values necessary to derive effect estimates, or (5) were not published in English. Reviews and meta-analyses were also excluded, but their bibliographies were searched. Reference lists of the included articles and studies that cited the included articles were examined for potential inclusion by D.E.O. In addition, meta-analyses on risk factors for CRC were examined to determine whether there were any studies that performed subgroup analyses among subjects younger than 50 years of age.

Data Extraction

D.E.O and R.L.S. extracted information on author, year of publication, geographic location, study design, sample size, definition of EoCRC, outcomes examined, sex of the participants, ethnicity of the participants, and risk factors examined. The referent category, effect estimates, and 95% confidence intervals (CIs) for exposure categories of each risk factor were extracted. Only effect estimates that were adjusted for at least age and sex were extracted. All of the extracted information was stored in an Excel file (Microsoft, Redmond, WA) and was checked for accuracy by D.E.O and R.L.S.

Study Quality Assessment

Study quality was evaluated by using a modified version of the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies.[15] The NOS is a quality scale that judges studies on the basis of 3 broad categories: (1) the selection of study groups, (2) the comparability of the groups, and (3) the ascertainment of exposure and outcome. In the original NOS, the comparability of the groups is scored either a 1 (adjusted for the most important confounder) or 0 (did not adjust for the most important confounder). Because this study was focused on a broad set of exposures, we modified this category to be scored from 0 to 2. A score of 2 corresponds to adjusting for the majority of established risk factors for CRC ($\geq$75% of the risk factors), a score of 1 corresponds to adjusting for a few established risk factors for CRC ($<$75% of the risk factors), and a score of 0 corresponds to adjusting for none of the established risk factors for CRC besides age and sex. A list of established risk factors that were considered is included in the Supplementary Material. Variables were considered adjusted for if eliminated from the final model through backwards elimination, stepwise selection, or change-in-estimate approaches. Because the NOS is only designed to evaluate study quality of case-control or cohort studies, we used an adapted version for the cross-sectional studies included in this review.[16] We categorized study quality on the basis of their total score: low (0–3), moderate (4–6), and high (7–9). D.E.O and R.L.S. rated the quality of the studies, and discrepancies were resolved through discussion and consensus.

Statistical Analysis

For the purposes of this study, hazard ratios and odds ratios were treated as estimates of relative risk. DerSimonian and Laird random-effect models were used to pool effect estimates for risk factors that were examined in at least 3 studies. Heterogeneity was investigated with the Q-test and I^2 statistics. Subgroup analyses or meta-regressions were not performed because of small numbers of studies included in each meta-analysis. To test for publication bias, we visually reviewed funnel plots and used Egger's weighted linear regression for meta-analyses that contained at least 5 studies.[17] We also used the trim and fill approach as a sensitivity analysis because the Egger's test is underpowered in meta-analyses with few studies.

For obesity, we pooled effect estimates for body mass index (BMI) greater than 30 kg/m^2 compared with the lowest referent category in each study (typically 18.5–24.9 kg/m^2). Two studies that examined BMI were not included in the obese BMI meta-analysis because one only examined BMI $\geq$25 kg/m^2 compared with $<$20 kg/m^2,[18] and the other examined BMI as a continuous variable.[19] The latter study did not provide enough information to determine an effect estimate for an obese BMI. For alcohol consumption, we pooled effect estimates for the highest study defined category compared with never drinkers. For cigarette smoking, we pooled effect estimates for the highest study defined category compared with never smoking. All analyses were performed by using the R computing framework (http://www.r-project.org).

Results

Study Inclusion and Characteristics of Included Studies

In total, 3304 unique articles were identified during the initial literature search, of which 177 articles plus 7 additional studies from reference lists underwent full-text review. After full-text review, a total of 20 studies examining at least one risk factor for EoCRC were retained, and 14 of these studies were included in the meta-analysis. The most common reasons for exclusion during the full-text review were lack of relevance (n = 82), incorrect study population (n = 31), or inappropriate comparator (n = 29) (Figure 1).

Characteristics of the 20 retained studies examining the risk of developing EoCRC associated with demographic characteristics, comorbidities, or lifestyle factors are presented in Table 1.[18-37] A total of 47,692 EoCRC cases were examined in these studies, with 6 of the 20 studies also examining subsites of CRC. Of the studies included in this review, 13 were conducted in North America, 3 in Europe, 3 in Asia, and 1 in Australia. Ten of the studies were case-control, 8 were cohort studies, and 2 were cross-sectional studies.

Study Quality

The majority of included studies were of moderate quality, with the exception of 6 studies that were deemed to be of high quality.[20,24,30,33,37] Most studies (n = 15) failed to adequately control for confounding, because few comprehensively adjusted for CRC risk factors. Nearly

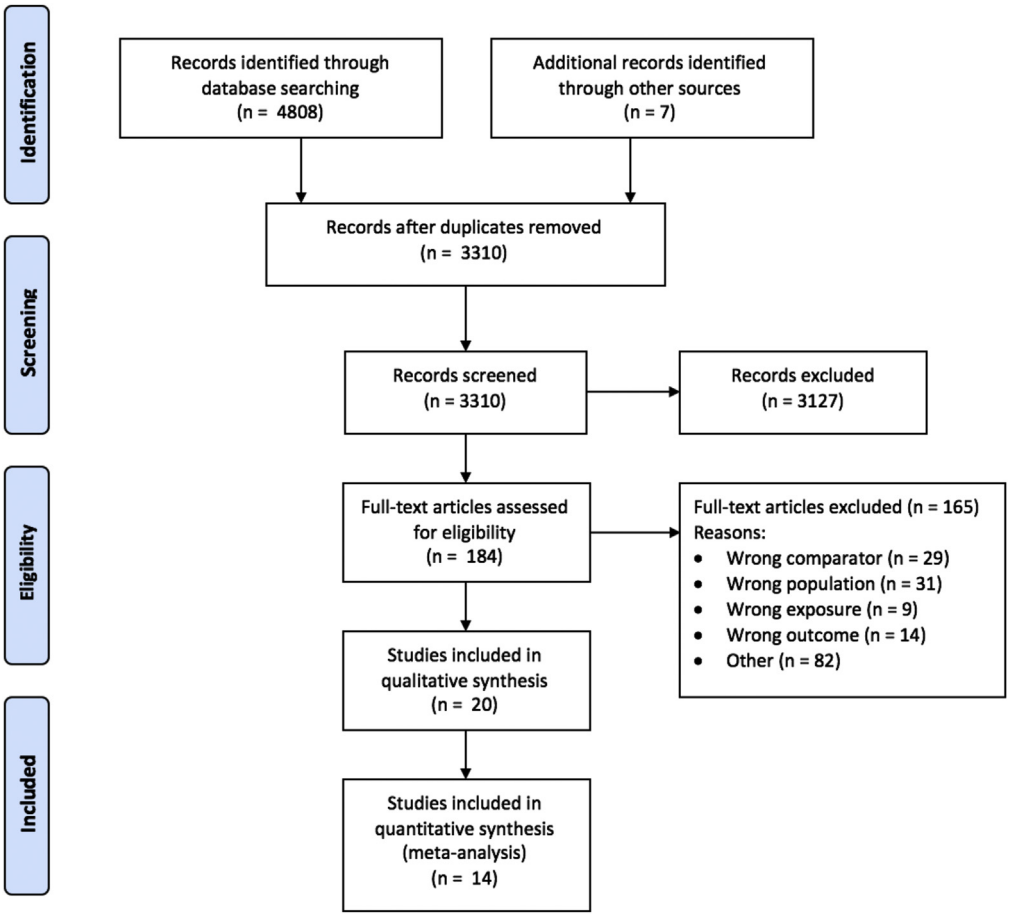

Figure 1. Flow diagram of selection procedure of studies assessing the relationship of various demographic characteristics, comorbidities, and lifestyle factors with the risk of developing early-onset colorectal cancer. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram that details the inclusion and exclusion of studies considered for this systematic review.

half of the case-control studies (n = 4) used hospital-based controls, and more than half of the cohort studies (n =5) used an unrepresentative cohort. Half of the studies (n = 10) used self-report to ascertain exposure to potential risk factors for EoCRC. A detailed description of study quality by specific domains of the modified NOS is presented in Supplementary Tables 1, 2, and 3.

Demographics

Ten studies examined the association of demographic factors with the development of EoCRC. The associations with the development of EoCRC for demographic factors that were examined in at least 3 studies are displayed in Figure 2. Male sex (pooled relative risk [RR] = 1.59; 95% CI, 1.23–2.07), Caucasian ethnicity (RR = 1.31; 95% CI, 1.06–1.62), and a history of CRC in a first-degree relative (RR = 4.21; 95% CI, 2.61–6.79) were all significantly associated with the development of EoCRC. There was considerable heterogeneity among risk estimates for all the examined demographic factors (I^2 >60%). There was some indication of publication bias as implied by the trim and fill method for male sex and Caucasian ethnicity (Supplementary Figures 1 and 2). There was little evidence of publication bias for the family history of CRC meta-analysis (Supplementary Figure 3). Two studies examined the relationship of education with the development of EoCRC, and the studies had conflicting results.[18,33] One study examined the relationship of age with the development of EoCRC and observed a significant increased risk with increasing age (continuous variable).[27] Three other studies presented enough information to obtain crude estimates for age, but the age cutoffs varied (Supplementary Table 4).

Comorbidities

A total of 9 studies examined the association between pre-existing comorbidities and the development of EoCRC. The associations with the development of EoCRC for comorbidities that were examined in at least 3 studies are displayed in Figure 3. Obesity (pooled RR = 1.54; 95% CI, 1.01–2.35) and hyperlipidemia (high levels of fat – cholesterol and triglycerides in the blood) (pooled RR = 1.62; 95% CI, 1.22–2.13) were both significantly associated with the development of EoCRC. There was considerable heterogeneity among study-specific estimates for both obesity (I^2 = 98.7%) and hyperlipidemia (I^2 = 96.8%). There was minimal evidence of publication bias for the obesity meta-analysis (Supplementary Figure 4). There was some evidence of plot asymmetry from visual inspection for the hyperlipidemia meta-analysis, but the trim and fill method did not indicate any missing studies (Supplementary Figure 5). Type 2 diabetes was examined in 3

Table 1. Characteristics of All Studies Investigating Risk Factors for the Development of Early-Onset (<50 Years of Age) Colorectal Cancer

Study and location	Study design (period)	Early-onset definition (*y*)	Outcome	Sample size (cases)	Sex (% *men*)	Ethnicity (% *Caucasian*)	Demographics	Comorbidities	Lifestyle factors
Chen et al, 2020 (United States)	Case-control (2006–2015)	<50	CRC, colon cancer (proximal and distal), rectal cancer	4673	51.3	NR	None	Metabolic syndrome	None
Dash et al, 2020 (United States)	Cohort (1995–2013)	<50	CRC	113	0.0	0.0	None	BMI, waist circumference, waist to hip, body shape index	Weight change
Elangovan et al, 2020 (United States)	Cross-sectional (2014–2019)	<50	CRC	16,090	41.7	58.8	None	BMI, diabetes, hypertension, hyperlipidemia	Smoking
Fauchs et al, 1994 (United States)	Cohort (1986–1992)	<50	CRC	13	0.0	NR	Family history of CRC	None	None
Gausman et al, 2019 (United States - New York)	Case-control (2011–2017)	<50	CRC	269	46.5	55.4	Sex, ethnicity, and family history of CRC	BMI and hyperlipidemia	None
Ghadirian et al, 1997 (Canada)	Case-control (1989–1993)	<50	Colon cancer	118	41.0	NR	Family history of CRC	None	None
Levi et al, 2017 (Israel)	Cohort (1967–2010)	<45	CRC	1089	100.0	0.0	None	BMI	None
L'Heureux et al, 2019 (Taiwan)	Case-control (2008–2013)	<50	CRC, colon cancer, rectal cancer	8623	57.2	0.0	None	Thyroid disorders	None
Liu et al, 2018 (United States)	Cohort (2004–2008)	<50	CRC, colon cancer, rectal cancer	114	0.0	NR	None	BMI	Weight change
Low et al, 2020 (United States)	Case-control (1999–2014)	<50	CRC	651	82.3	55.3	Age and sex	BMI, diabetes, iron deficient anemia	Weight loss, smoking, aspirin use
Negri et al, 1998 (Italy)	Case-control (1992–1996)	<45	CRC, colon cancer, rectal cancer	145	52.4	NR	Family history of CRC	None	None

Table 1. Continued

Study and location	Study design (period)	Early-onset definition (*y*)	Outcome	Sample size (cases)	Sex (% *men*)	Ethnicity (% *Caucasian*)	Demographics	Comorbidities	Lifestyle factors
Nguyen et al, 2019 (United States)	Cohort (1991–2011)	<50	CRC, colon cancer, rectal cancer	118	0.0	92.0	None	None	Sedentary behavior
Peters et al, 1989 (United States - LA County)	Case-control (1974–1982)	<45	CRC, stratified (right-sided, traverse/ descending, sigmoid, rectum)	147	100.0	89.1	None	None	Diet, smoking, alcohol, occupational physical activity, dust exposure, chemical exposure, inhaled substance exposure
Rosato et al, 2013 (Italy and Switzerland)	Case-control (1985–2009)	<45	CRC	329	53.4	NR	Education, family history of CRC	BMI, diabetes	Alcohol, physical activity, diet, vitamins
Samadder et al, 2015 (United States - Utah)	Case-control (1980–2010)	<50	CRC	7344	52.7	NR	Family history	None	None
Sanford et al, 2019 (United States)	Cross-sectional (1998–2017)	<50	CRC	239	44.1	79.5	Sex and ethnicity	BMI	Smoking
Sondergaard et al, 2013 (Denmark)	Cohort (1978–2009)	<45	CRC	1789	NR	NR	Education	None	None
St John et al, 1993 (Australia)	Case-control (1952–1985)	<45	CRC	82	47.8	NR	Family history	None	None
Syed et al, 2019 (United States)	Cohort (2012–2016)	<50	CRC	5710	NR	NR	Sex, ethnicity, family history of cancer, family history of CRC, family history of polyps	BMI, colitis, hypertension, hyperlipidemia	Tobacco use, alcohol use
Wu et al, 2013 (Taiwan)	Cohort (2004–2005)	<50	CRC	36	52.0	0.0	None	Chronic kidney disease	None

BMI, body mass index; CRC, colorectal cancer; NR, not reported.

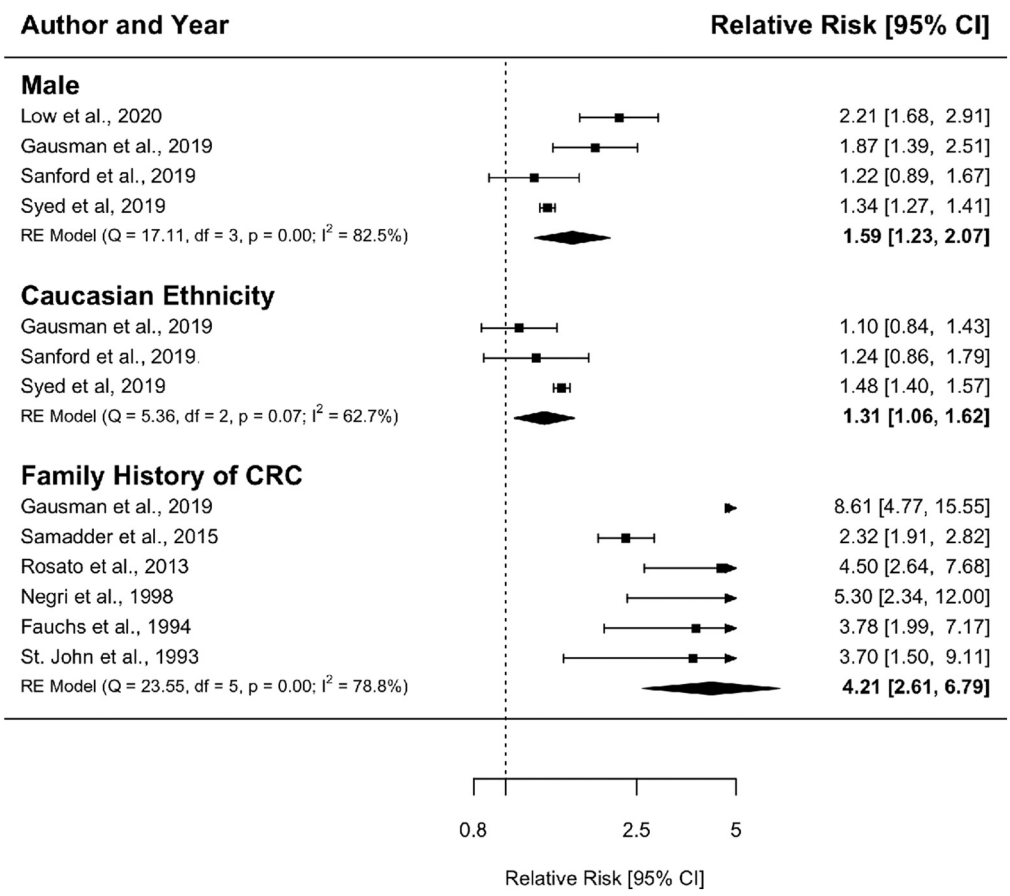

Figure 2. Estimated relative risk of developing early-onset colorectal cancer associated with male sex, Caucasian ethnicity, and a family history of colorectal cancer. CI, confidence interval; CRC, colorectal cancer.

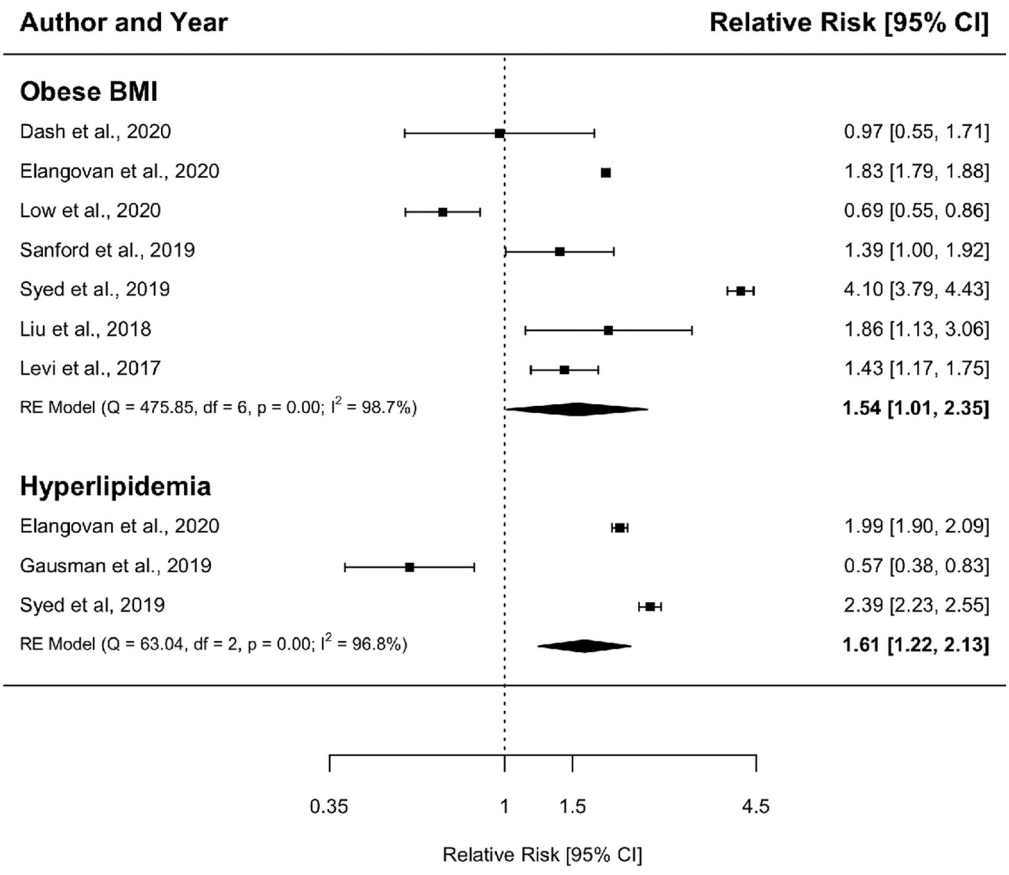

Figure 3. Estimated relative risk of developing early-onset colorectal cancer associated with an obese BMI and hyperlipidemia. BMI, body mass index; CI, confidence interval.

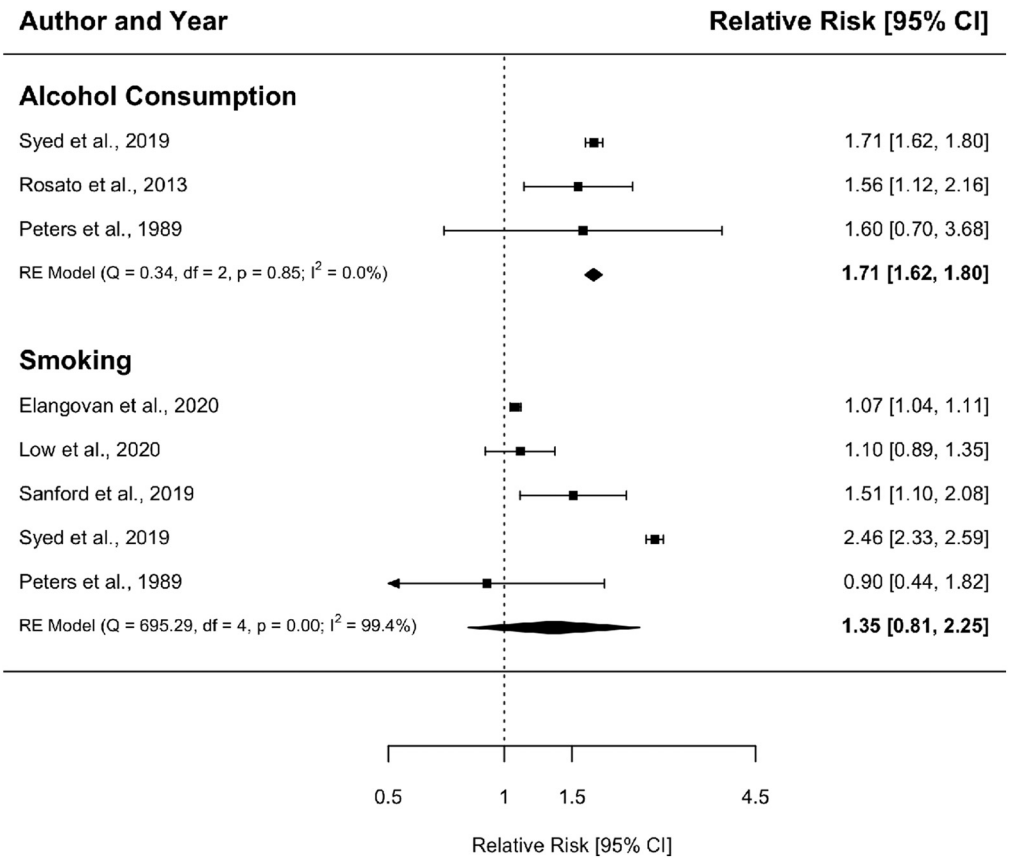

Figure 4. Estimated relative risk of developing early-onset colorectal cancer associated with alcohol consumption and a history of smoking. CI, confidence interval.

studies,[18,21,27] but only 2 of the studies reported effect estimates associated with the development of EoCRC; one study observed a higher risk,[21] and the other reported a null association.[18] Among the remaining studies, a significantly higher risk of developing EoCRC was associated with hypertension,[21,35] metabolic syndrome,[37] ulcerative colitis,[35] and chronic kidney disease,[35] whereas a lower risk was associated with hyperthyroidism.[25]

Lifestyle Behaviors and Occupational Factors

Nine studies examined the association of lifestyle or occupational factors with the development of EoCRC. The associations with the development of EoCRC for lifestyle factors that were examined in at least 3 studies are displayed in Figure 4. Alcohol consumption was significantly associated with the development of EoCRC (pooled RR = 1.71; 95% CI, 1.62–1.80), but cigarette smoking was not significantly associated (pooled RR = 1.35; 95% CI, 0.81–2.25). There was considerable heterogeneity among studies included in the meta-analysis for cigarette smoking (I^2 = 99.4%) but not for alcohol consumption (I^2 = 0.0%). There was minimal evidence of publication bias for both of the meta-analyses (Supplementary Figures 6 and 7).

Among the remaining studies, a significantly higher risk of developing EoCRC was associated with sedentary behavior,[29] processed meat consumption,[18] and occupational exposure to organic dusts,[9] and suggestive higher risks were associated with sedentary occupations[30] and consumption of fried food.[30] A significantly lower risk of developing EoCRC was associated with fruit and vegetable consumption,[18,30] fish consumption,[18] B-carotene,[18] vitamin C,[18] vitamin E,[18] folate,[18] and aspirin use.[27] Physical activity[30] and red meat consumption[17] were unrelated to the development of EoCRC.

Discussion

In this systematic review and meta-analysis, male sex, Caucasian ethnicity, CRC history in a first-degree relative, hyperlipidemia, obesity, and alcohol consumption were all significantly associated with a higher risk of developing EoCRC. Smoking was a suggestive but statistically non-significant risk factor. With the exception of alcohol consumption, there was considerable heterogeneity among included studies. Other potential risk factors that were less studied included ulcerative colitis, chronic kidney disease, hypertension, diet-related factors, sedentary behavior, and occupational exposure to organic dusts.

Despite several recent reviews on EoCRC[8,38] including the clinical management of EoCRC[10] and society-endorsed reductions in the age of screening in an attempt to address its incidence,[39,40] there is little knowledge of risk factors for the development of EoCRC. In this study, we identified several potential risk factors that could be used for primary and secondary prevention

of EoCRC and should be investigated in future studies. For instance, several risk factors for CRC were associated with EoCRC, and dissemination of these results to the public could motivate behavioral change. This is especially true because early-onset cancers tend to be diagnosed at later stages, result in more quality life years lost, and can have long-term health consequences.[10] In addition, awareness of risk factors for EoCRC can motivate physicians and their patients to be more vigilant of early symptoms of CRC, such as rectal bleeding, weight loss, changes in bowel habits, abdominal pain, or iron deficiency.[10] Finally, these potential risk factors should be used to create simple prediction models for EoCRC that could be used for targeted screening of high-risk groups, therefore reducing the incidence of EoCRC without a widespread change in the age of onset for screening.

Family history of CRC in a first-degree relative has been shown to double the overall risk of CRC,[41] but this meta-analysis indicates that family history may be a stronger risk factor for EoCRC. Individuals with a family history of CRC are already recommended to undergo earlier screening compared with the general population,[10] but future studies should examine whether a family history of other cancers before the age of 50 is associated with an increased risk of EoCRC. Studies examining the family history of other cancers could lead to more refined targeted screening strategies, particularly if there is a young-onset phenotype. Hyperlipidemia was the only comorbidity that could be examined in a meta-analysis and was significantly associated with the development of EoCRC. Hyperlipidemia has been shown to be a risk factor for CRC in general,[42] and the results from this study indicate that it could be a stronger risk factor for EoCRC. More studies are required to confirm hyperlipidemia as a risk factor for EoCRC, and future studies should examine the utility of incorporating cholesterol levels in prediction models for identifying individuals at high risk for EoCRC, individuals who may benefit from earlier screening. Inflammatory bowel disease,[43] type 2 diabetes,[44] and hypertension[45] have all been consistently associated with the development of CRC but have been understudied for EoCRC and require confirmation as risk factors. Interestingly, one study examined the risk of CRC associated with chronic kidney disease and observed a larger increased risk for EoCRC compared with adults older than the age of 50.[36] More studies are required to confirm this relationship, but patients younger than 50 with chronic kidney disease may benefit from earlier screening or enhanced surveillance of early symptoms of CRC.

Several studies have hypothesized that obesity is responsible for the increase in EoCRC, because increases in the prevalence in obesity have occurred in parallel with the increase in the incidence of EoCRC.[46,47] In this study we found that an obese BMI was significantly related to the development of EoCRC, but there was considerable heterogeneity among risk estimates. Among the included studies, all reported an increased risk of EoCRC associated with obesity, with the exception of 2 studies.[20,27] Low et al[27] observed a lower risk of EoCRC associated with obesity; however, BMI was measured at diagnosis, and weight loss is a symptom of CRC. Dash et al[20] observed a null relationship for obesity with the development of EoCRC in a high-quality cohort study from the Black Women's Health Study. The lack of a relationship in that study may indicate a differential relationship by sex and ethnicity that should be explored in future studies. Despite only 3 studies examining the influence of alcohol consumption on the development of EoCRC, all studies observed similar increased risks of EoCRC associated with high levels of alcohol consumption. A relationship of EoCRC with alcohol consumption is plausible because alcohol consumption has been increasing in several countries including Canada[48] and the United States.[49] Future studies should examine the relationship of binge drinking with the development of EoCRC, because there has been a generational shift in the proportion of young adults attending college and universities where binge drinking is highly prevalent.[50]

Breau and Ellis previously published a meta-analysis that examined the associations of clinical and lifestyle factors with the development of early-onset colorectal adenomas and cancer combined. In this study they observed significant associations for alcohol consumption, smoking, obesity, elevated blood glucose, elevated blood pressure, and elevated triglycerides from combining results of 6 studies. It is important to note that only 2 of the included studies examined associations with EoCRC alone, which is important because not all adenomas develop into CRC. In contrast, our study included 12 studies that examined associations of clinical and lifestyle factors with EoCRC alone and observed significant associations with hyperlipidemia, obesity, and alcohol consumption. In addition, we also included 10 studies that examined the association of demographic factors with EoCRC, which is informative for risk-stratified screening of EoCRC.

Several future research directions are warranted in response to the increasing incidence of EoCRC. First, large observational studies on generalizable populations that comprehensively examine potential risk factors are required. Second, studies that include participants of various ages should compare the magnitude of risk associated with different risk factors between EoCRC and later-onset CRC cases to determine factors that are most strongly related to EoCRC. Third, studies that examine nontraditional risk factors, occupational exposures, and exposures that occur early in the life course are necessary to determine whether there are exposures unique to recent cohorts that are driving this increase. Fourth, simple prediction models for EoCRC should be explored because these models could be used for targeted screening of high-risk groups. Fifth, molecular studies on the genetic and epigenetic profiles of EoCRC tumors could inform on the etiology and treatment of EoCRC. Finally,

studies on treatment patterns and clinical outcomes of EoCRC using real-world data are necessary to ensure that these patients are receiving optimal treatment. Indeed, because clinical trials are unlikely to occur for this patient population, target trial emulations using real-world data[51] could identify optimal treatment strategies for EoCRC and ensure that patients are not overtreated, which can have several long-term consequences.[10]

Our study has limitations. First, our search terms were limited to the title and abstract, because expanding to the entire text would have resulted in more than 100,000 articles to be reviewed. However, this strategy does leave the systematic review susceptible to missing studies on CRC that included a subgroup analysis for participants younger than the age of 50 within the body of the text. To mitigate this issue, we reviewed all reference lists of the included studies, all studies that referenced the included studies, and examined previous meta-analyses on CRC risk factors to determine whether there were any studies with subgroup analyses younger than the age of 50. This strategy only identified additional studies for the risk of EoCRC associated with a family history of CRC. We did find additional studies that examined age effects, but these studies either examined a young age group that included individuals older than the age of 50 or compared the average age of onset across exposure groups. There is some chance that studies where an occupational exposure was examined in relation to multiple cancer types were missed. However, because most research on EoCRC has occurred recently, we are confident that the probability of missing a study with our search strategy was low overall. Second, we only included studies that were published in English, which makes it possible that there were some non-English studies that were omitted. Third, despite there being a high degree of heterogeneity in the risk estimates across studies for the majority of risk factors, we were unable to explore sources of this heterogeneity (including differences in study design, study quality, or control for confounding) because of an insufficient number of studies included in each meta-analysis. Furthermore, the majority of included studies were of modest quality, suggesting that the results of this study could be biased and subject to residual confounding. Fourth, because of the small number of studies included in each meta-analysis, it was difficult to determine whether publication bias was present with formal methods; therefore, publication bias cannot be ruled out for any of the analyses. Finally, many of the studies included in this meta-analysis were conducted on unique study populations, which make the results difficult to generalize to heterogeneous populations where targeted screening approaches would be administered. Although some of the studies date back to the 1950s, the effect estimates here present increased risk related to exposure. If the exposures here are indeed true etiologic risk factors, then their increasing or changing prevalence over time may be what is driving increases in rates. Thus, although the baseline risk in older studies may be lower, the RR related to the exposure should still be valid.

In conclusion, male sex, Caucasian ethnicity, CRC history in a first-degree relative, hyperlipidemia, obesity, and alcohol consumption appear to be risk factors for EoCRC. High-quality studies conducted on generalizable populations and that comprehensively examine risk factors for EoCRC are required to inform primary and secondary prevention initiatives for EoCRC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.01.037.

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Susanna Town (Conceptualization: Supporting; Data curation: Lead; Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Equal)

Kristian Chow (Conceptualization: Supporting; Data curation: Lead; Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Equal)

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Robert J. Hilsden (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Methodology: Equal; Resources: Supporting; Supervision: Supporting; Writing – review & editing: Equal)

Darren R. Brenner (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Methodology: Lead; Resources: Lead; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Lead)

Conflicts of interest
The authors disclose no conflicts.

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Supplementary Material

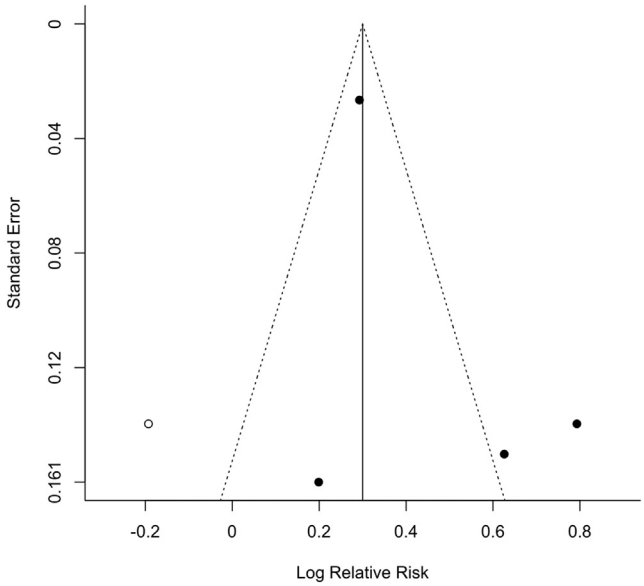
Search Strategy

Databases: MEDLINE and Embase

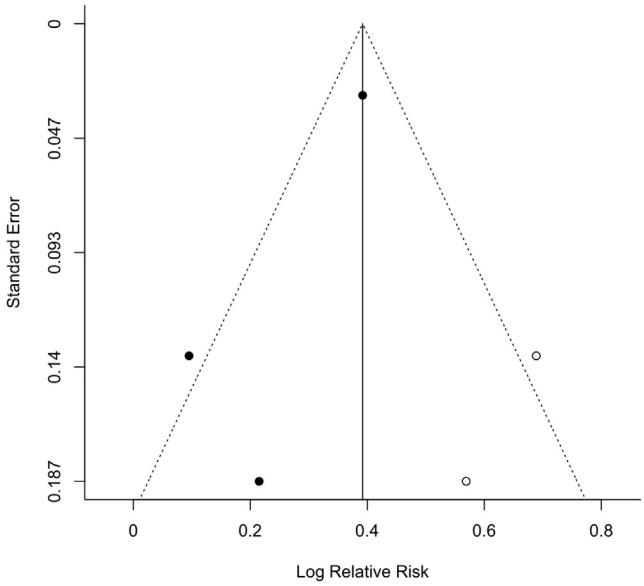
1. exp colorectal neoplasms/ or exp adenomatous polyposis coli/ or exp colonic neoplasms/ or exp colorectal neoplasms, hereditary nonpolyposis/ or exp rectal neoplasms/
2. ("colon tumo?r" or "colon dysplasia*" or "colon malign*" or "colon canc*" or "rect* tumo?r" or "rect* dysplasia*" or "rect* malign*" or "rect* canc*" or "colorectal tumo?r" or "colorectal dysplasia*" or "colorectal malign*" or "colorect* canc*" or "gastro* canc*" or CRC).ti,ab
3. ("young onset" or "early onset" or "young adult*" or "early-onset" or "young-onset" or "AYA" or adolescen* or "under 50" or "under the age of 50" or "younger than 50" or "49 and younger" or "15-49" or "under 40" or "under the age of 40" or "younger than 40" or "under 30" or "under the age of 30" or "younger than 30" or "under 20" or "under the age of 20" or "younger than 20").ti,ab.
4. (risk* or "risk* factor*" or "determinant*" or "cause*" or associat* or relat* or factor*).ti.
5. 1 or 2
6. 3
7. 4 or 5
8. 5 and 6 and 7
9. Remove duplicates from 8
10. Limit 9 to animals
11. Limit 8 to (animals and humans)
12. 10 not 11
13. 9 not 12
14. Limit 13 to (case reports or comment or editorial or letter or review or congress)
15. 13 not 14

Established Risk Factors for Colorectal Cancer Considered in Confounding Criteria for the Newcastle-Ottawa Scale

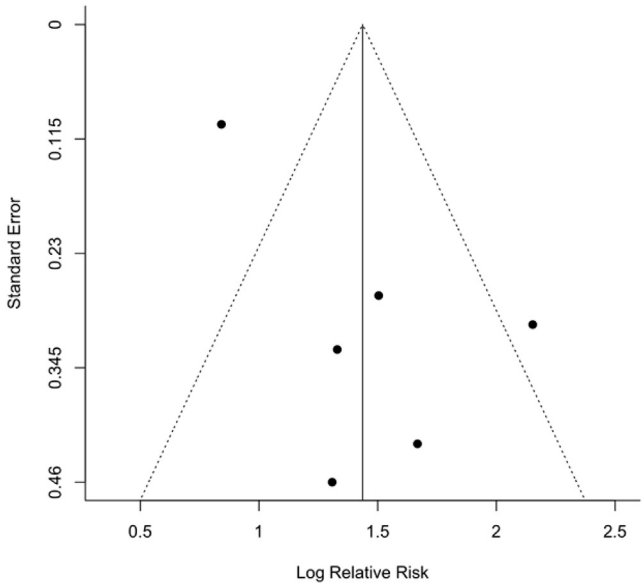
Age, sex, family history of CRC, ethnicity or race, personal history of polyps, inflammatory bowel disease, diabetes, obesity, alcohol consumption, smoking, physical inactivity, fruit and vegetable consumption, processed and red meat consumption, and sedentary behavior.



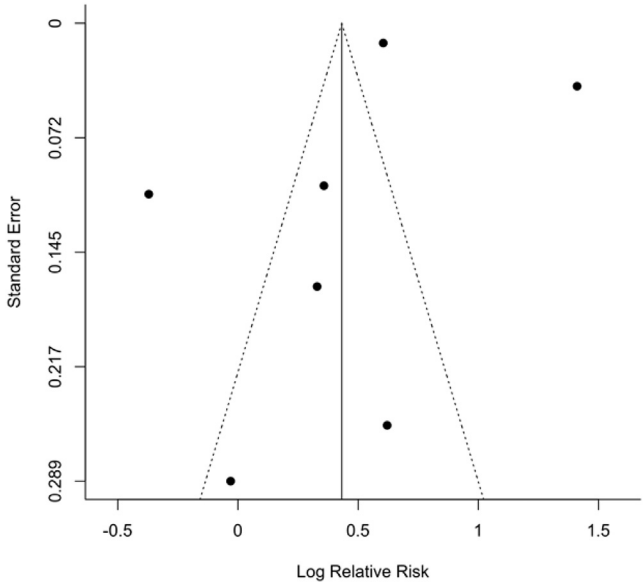
Supplementary Figure 1. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with male sex. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis. *White dot* corresponds to one unpublished study suggested by the trim and fill method. The inclusion of this study changed the summary estimate to 1.35 (95% CI, 1.29–1.42) from 1.37 (95% CI, 1.31–1.44). CI, confidence interval.



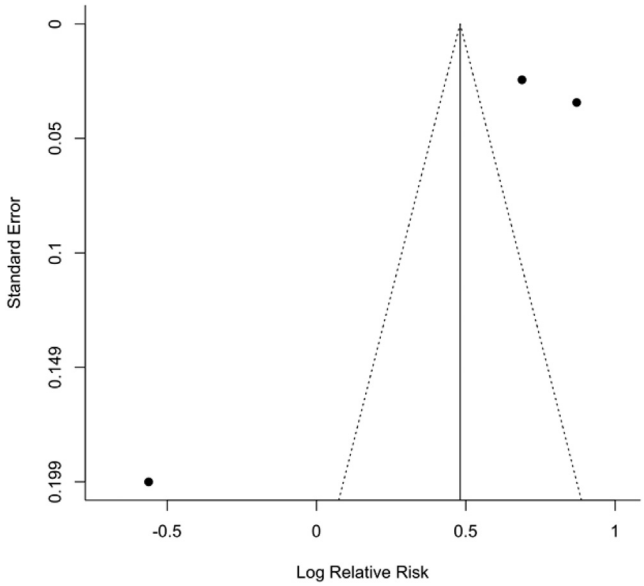
Supplementary Figure 2. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with Caucasian ethnicity. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis. *White dots* correspond to 2 unpublished studies suggested by the trim and fill method. The inclusion of these studies changed the summary estimate to 1.48 (95% CI, 1.24–1.77) from 1.31 (95% CI, 1.07–1.62). CI, confidence interval.



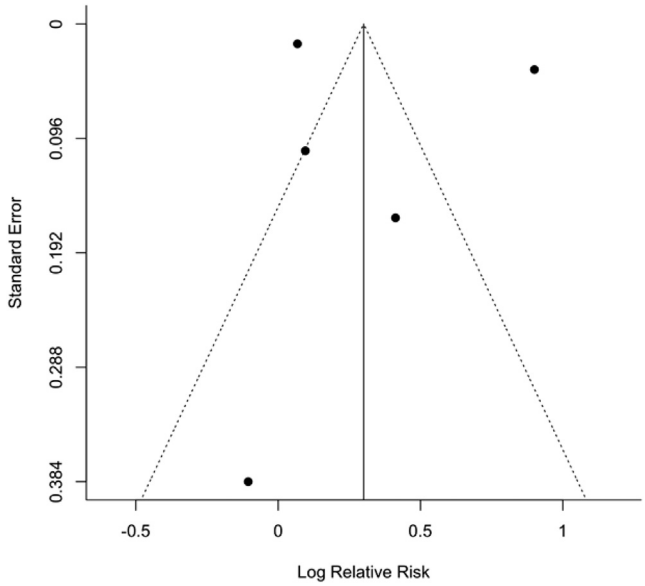
Supplementary Figure 3. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with family history of colorectal cancer. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis.



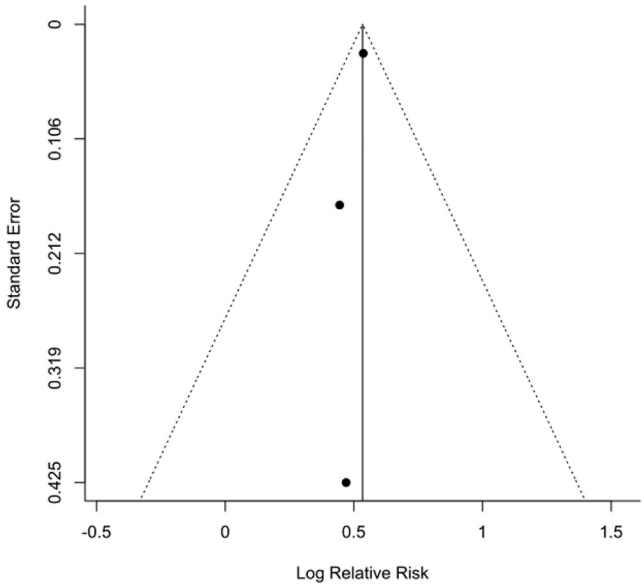
Supplementary Figure 4. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with obesity. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis.



Supplementary Figure 5. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with hyperlipidemia. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis.



Supplementary Figure 7. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with smoking. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis.



Supplementary Figure 6. Funnel plot of relative risk estimates for early-onset colorectal cancer associated with alcohol consumption. *Outer dashed lines* indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. *Solid black line* corresponds to the summary effect estimate. *Black dots* correspond to studies included in this analysis.

Supplementary Table 1. Evaluation of Study Quality and Risk of Bias for Case-Control Studies Included in the Systematic Review

Author	Case	Representative	Controls	Definition	Confounding	Exposure	Method	Nonresponse	Score
Chen et al, 2020	1	1	1	1	1	1	1	1	8
Gausman et al, 2019	1	1	0	1	1	0	1	1	5
Ghadirian et al, 1997	1	1	1	1	0	1	1	0	6
L'Heureux et al, 2019	1	1	0	1	1	0	1	1	4
Low et al, 2020	1	0	1	1	1	0	1	1	5
Negri et al, 1998	1	1	1	1	0	0	1	1	6
Peters et al, 1989	1	1	1	1	0	1	1	1	7
Rosato et al, 2013	1	1	0	1	2	1	1	1	6
St John et al, 1993	1	1	0	1	0	1	1	1	6
Samadder et al, 2015	1	1	1	1	0	1	1	1	7

NOTE. All categories were scored on the basis of the Newcastle-Ottawa Scale with the exception of the category "Control for confounding". Confounding: a score of 2 corresponds to adjusting for the majority of established risk factors for CRC (≥75% of the risk factors), a score of 1 corresponds to adjusting for a few established risk factors for CRC (<75% of the risk factors), and a score of 0 corresponds to adjusting for none of the established risk factors for CRC besides age and sex. The summary score for each study was calculated by summing the score from each category.
CRC, colorectal cancer.

Supplementary Table 2. Evaluation of Study Quality and Risk of Bias for Cohort Studies Included in the Systematic Review

Author	Representative	Nonexposed	Exposure	Outcome not present	Confounding	Outcome	Follow-up	Adequate follow-up	Score
Dash et al, 2020	0	1	0	1	2	1	1	1	7
Faucs et al, 1994	0	1	0	1	2	1	1	1	5
Levi et al, 2019	1	1	1	1	0	1	1	1	7
Liu et al, 2018	0	1	0	1	2	1	1	1	5
Nguyen et al, 2019	0	1	0	1	2	1	1	1	5
Sondergaard et al, 2013	1	1	1	1	0	1	1	1	7
Syed et al, 2019	0	1	0	1	0	0	1	1	4
Wu et al, 2013	1	1	1	1	0	1	0	1	6

NOTE. All categories were scored on the basis of the Newcastle-Ottawa Scale with the exception of the category "Control for confounding". Confounding: a score of 2 corresponds to adjusting for the majority of established risk factors for CRC (≥75% of the risk factors), a score of 1 corresponds to adjusting for a few established risk factors for CRC (<75% of the risk factors), and a score of 0 corresponds to adjusting for none of the established risk factors for CRC besides age and sex. The summary score for each study was calculated by summing the score from each category.
CRC, colorectal cancer.

Supplementary Table 3. Evaluation of Study Quality and Risk of Bias for Cross-Sectional Studies Included in the Systematic Review

Author	Representative	Sample size	Non-respondents	Exposure	Control for confounding	Outcome	Statistical test	Score
Elangovan et al, 2020	0	1	0	0	0	1	1	4
Sanford et al, 2019	1	1	0	1	0	0	1	4

NOTE. All categories were scored on the basis of the adapted version of the Newcastle-Ottawa Scale for cross-sectional studies with the exception of the category "Control for confounding". Confounding: a score of 2 corresponds to adjusting for the majority of established risk factors for CRC (≥75% of the risk factors), a score of 1 corresponds to adjusting for a few established risk factors for CRC (<75% of the risk factors), and a score of 0 corresponds to adjusting for none of the established risk factors for CRC besides age and sex. The summary score for each study was calculated by summing the score from each category. CRC, colorectal cancer.

Supplementary Table 4. Studies Examining the Effect of Age on the Development of Colorectal Cancer Before Age of 50

Study	Age analysis	Adjusted	Effect estimate (95% confidence interval)
Elangovan et al, 2020	40–49 vs 20–39	No	0.75 (0.72–0.78)
Levi et al, 2017	36–45 vs <36	No	6.14 (5.42–6.95)
Low et al, 2020	Continuous per year increase	Yes	1.05 (1.03–1.07)
Syed et al, 2019	40–49 vs 25–39	No	4.20 (3.95–4.45)