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Risk Factors Associated With Young-Onset Colorectal Adenomas and Cancer: A Systematic Review and Meta-Analysis of Observational Research

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Abstract

The risk of young-onset colorectal adenomas and cancer (yCRAC) in adults less than 50 years of age is increasing. We conducted a systematic review and meta-analysis of epidemiologic studies to identify lifestyle and clinical risk factors associated with yCRAC risk. We searched Medline, EMBASE, and Cochrane Database of Systematic Reviews for studies which: used an epidemiologic study design, involved individuals with yCRAC, evaluated at least 1 lifestyle or clinical factor, and applied multivariable regression approaches. We critically appraised the quality of included studies and calculated pooled measures of association (e.g. odds ratio [OR]) and 95% confidence intervals (CI) using random-effects models. We identified 499 articles in our search with 9 included in a narrative synthesis and 6 included in a meta-analysis. We found in the pooled analysis that smoking and alcohol consumption were lifestyle factors associated with yCRAC, as were clinical factors including obesity elevated blood glucose, elevated blood pressure, and elevated triglycerides. We identified lifestyle and clinical risk factors associated with risk of yCRAC, which have potential implications for informing preventive efforts and modifying screening to target at-risk populations.

Keywords

colorectal cancer, hypertension, meta-analysis, metabolic disorder, type II diabetes, young adult cancer

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Highlights

What Do We Already Know About This Topic?

Young-onset (diagnosis before age of 50 years) colorectal adenomas and cancer (yCRAC) incidence is increasing, although current population-based screening programs do not always capture this group. It is necessary to identify whether subgroups of individuals under the age of 50 years are at increased risk of yCRAC, in order to enhance surveillance for certain groups at increased risk due to lifestyle and clinical factors and comorbid chronic conditions.

How Does This Research Contribute to the Cancer Control Field?

In this systematic review and meta-analysis, we identify 2 lifestyle factors (smoking, alcohol consumption), 4 clinical factors (obesity, elevated blood glucose, elevated blood pressure, elevated triglycerides) and 2 chronic conditions (type II diabetes, metabolic syndrome) which are associated with yCRAC diagnosis and advanced yCRAC diagnosis.

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What Are Our Research's Implications Toward Theory, Practice, or Policy?

Given our findings from our systematic review and meta-analysis, we suggest that clinicians and policy makers should consider making population-based colorectal cancer screening programs available to younger adults with certain risk factors and/or comorbid diseases that place them at greater risk of yCRAC. Current colorectal cancer screening programs do not currently capture all individuals at greater risk, which may be contributing to the greater incidence of yCRAC currently observed.

Introduction

Colorectal cancer (CRC) is a heterogeneous disease of the colon and rectum that typically develop from adenomatous polyps or adenomas.[1] In 2018 it was reported that of the 18.1 million new cases of cancer, CRC accounted for 10.2% and among 9.6 million cancer-related deaths, CRC accounted for 9.2%.[2] CRC has negative impacts on physical health,[3] life expectancy,[4] finances,[5] and psychosocial health.[6]

Generally CRC has been considered a disease of older adults, with the Canadian Task Force on Preventive Health Care recommending screening for adults aged 50 years and older, and the American Cancer Society recommending screening for adults aged 45 years and older.[7,8] However, there is growing evidence that the risk of young-onset CRC and adenoma (yCRAC) in adults under the age of 50 years is increasing. In 2019, using data from Cancer Incidence in Five Continents, Siegel et al. showed increasing risk of yCRAC particularly in high-income countries with cross-sectional age-standardized CRC incidence for adults 20-49 years ranging from 3.5 (95% confidence interval [CI] 3.2 to 3.9) per 100,000 in India to 12.9 (95% CI 12.6-13.3) per 100,000 in Korea, with the average annual percentage change (AAPC) as high as 4.2 (95% CI 3.4-5.0).[9]

Despite these data on increasing risk of yCRAC, reasons for this increase have not been systematically evaluated. With respect to CRC at any age at diagnosis, certain modifiable risk factors have been found to be predictive of CRC onset. In their 2017 review, Kerr et al. reported obesity as a risk factor for CRC[10] which was supported by Avgerinos et al. who in 2019 proposed potential biological mechanisms linking obesity to CRC, including abnormalities in signaling pathways, the role of insulin-like growth factors, sex hormones, and adipocytokines, chronic low-grade inflammation, and alterations in circadian rhythms and nutrient intake.[11] More recently, a 2019 review by Murphy et al.[12] reported that obesity, smoking, and alcohol consumption are predictors of CRC onset. However, no review to date has examined which risk factors are related to yCRAC, especially in light of aforementioned increasing risk. Thus, our objective was to conduct a systematic review and meta-analysis of epidemiological studies examining risk factors associated with yCRAC.

Methods

Search Strategy and Study Selection

We searched Ovid MEDLINE (1946-present), Ovid EMBASE (1974-present), and the Cochrane Database of Systematic Reviews via Ovid (1995-present) in May 2019 for peer-reviewed studies, published in English, that met the following criteria: used an epidemiologic study design (e.g. cohort, case control, and cross-sectional design), included a population or sample of individuals with yCRAC, primarily under the age of 50 years but considering other age cut-offs, and evaluated risk factors for yCRAC which for purposes of our study we are defining according to the World Health Organization as factors that increase the likelihood of an individual developing a disease.[13] Furthermore, for our purposes we considered as risk factors: 1) lifestyle related factors (e.g. smoking, alcohol consumption); 2) clinical factors (e.g. obesity, elevated blood glucose levels, elevated blood pressure, and elevated triglycerides); and 3) comorbid conditions (e.g. type 2 diabetes, metabolic syndrome). We further restricted our inclusion for studies that assessed independent associations between risk factors and yCRAC, based on the use of multivariable regression methods in analyses. Our search strategy for MEDLINE and EMBASE databases is given in Table 1, was designed by a health sciences librarian, and was conducted in May 2019. The searches were conducted again in November 2019 using the same search methods, and no new studies meeting inclusion criteria were identified. We conducted backward hand searching for all systematic reviews identified in the database searches and hand searched reference lists of included articles. Title and abstract screening, and full-text screening, was conducted by the first author. The first author discussed whether to include articles that passed full-text screening with an independent researcher.

Data Extraction and Data Analysis

We extracted information on study characteristics including year and country of publication, age range to define yCRAC, sample size, and sex distribution. We extracted information on the type of risk factor (e.g. smoking, blood glucose level, type 2 diabetes), method for assessing the risk factor (e.g., self-report, measurement by a clinician), measurement of the risk factor (e.g., consumption levels for lifestyle factors, cut-off values for clinical factors, diagnostic criteria for comorbidities), and reported univariate and multivariable measures of association (e.g., odds ratio [OR], relative risk [RR]) and corresponding 95% CI with yCRAC.

We conducted a narrative synthesis of findings from included studies. Additionally, where similar measures of association for a risk factor were reported in at least 2 studies, we included these in subsequent meta-analyses to calculated pooled measures of association and 95% CIs. We used STATA version 15 software for the meta-analysis.[14]

Table 1. Search Strategy for MedLine and Embase.

	Terms
Medline search	
1	colorectal neoplasms/ or adenomatous polyposis coli/ or colonic neoplasms/ or sigmoid neoplasms/ or rectal neoplasms/ or duodenal neoplasms/ or ileal neoplasms/ or jejunal neoplasms/
2	((colon or Rect*) adj3 (cancer* or neoplasm*)).tw, kf.
3	(colorectal adj3 (cancer* or neoplasm*)).tw, kf.
4	1 or 2 or 3
5	risk/ or logistic models/ or protective factors/ or risk factors/
6	(risk or protective or determinants).tw, kf.
7	5 or 6
8	4 and 7
9	case-control studies/ or retrospective studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or cross-sectional studies/
10	(cohort or case control or cross-sectional).tw, kf.
11	9 or 10
12	8 and 11
13	"age of onset"/
14	(early onset or young onset).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15	13 or 14
16	12 and 15
17	young.tw, kf.
18	13 or 14 or 17
19	12 and 18
Embase search	
1	colorectal neoplasms/ or adenomatous polyposis coli/ or colonic neoplasms/ or sigmoid neoplasms/ or rectal neoplasms/ or duodenal neoplasms/ or ileal neoplasms/ or jejunal neoplasms/
2	colorectal tumor/ or exp colon tumor/ or exp rectum tumor/ or colorectal adenoma/
3	((colon or rect* or colorectal) adj3 (cancer* or neoplasm*)).tw, kw.
4	1 or 2 or 3
5	risk/ or logistic models/ or protective factors/ or risk factors/
6	risk factor/
7	(risk or protective or determinants).tw, kw.
8	5 or 6 or 7
9	case-control studies/ or retrospective studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or cross-sectional studies/
10	case control study/ or population based case control study/ or cohort analysis/ or cross-sectional study/
11	(cohort or case control or cross-sectional).tw, kw.
12	9 or 10 or 11
13	"age of onset"/
14	onset age/
15	(early onset or young).tw, kw.
16	13 or 14 or 15
17	4 and 8 and 12 and 16

Quality Assessment

Quality assessment was conducted by 2 researchers using the Newcastle-Ottawa Quality Assessment Scales for case control studies, cohort studies, and cross-sectional studies.[15,16] The scale used depends on the study design and studies were rated on a numerical score of a maximum of 8 (for cohort and case-control studies) or 7 (for cross-sectional studies). The assessments were based on: case and control selection, comparability of the cases and controls, and methods for ascertainment of the exposure of cases and controls to the risk factor of interest (case control studies) and outcome (cohort and cross-sectional studies). A score above 5 is considered "Good" quality, 3 to 5 "Fair" quality, and 0 to 2 "Poor" quality.[17]

Results

Study Selection and Characteristics

Initial searches identified 989 articles, with an additional article identified through backward reference searching (see Figure 1). Once duplicates were removed, 499 articles underwent title and abstract screening, and 27 articles underwent full-text screening. Nine articles were included in the narrative synthesis, and

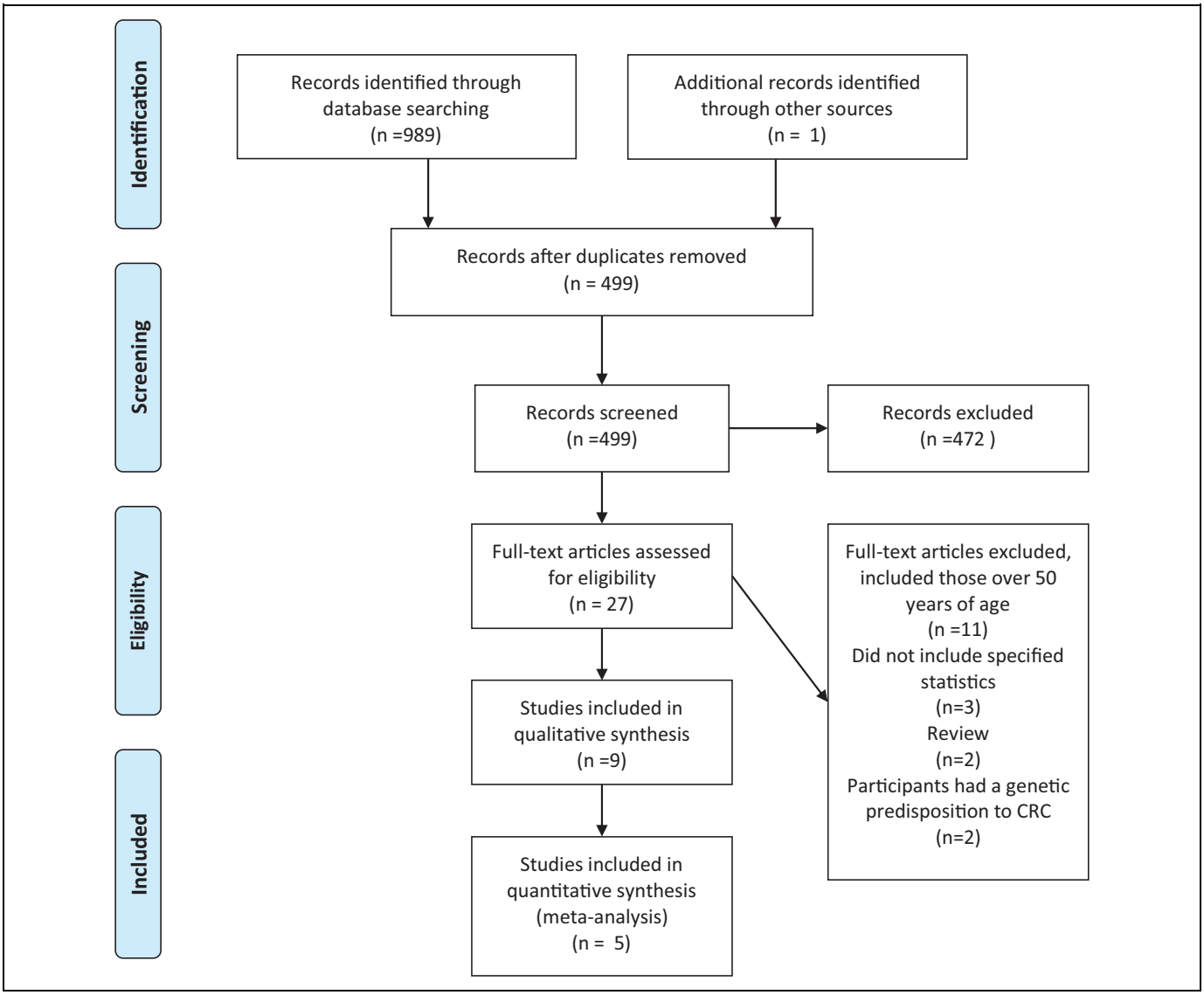

Figure 1. PRISMA diagram for systematic literature search.

6 articles were included in the meta-analysis. Table 2 summarizes study characteristics including quality assessment scores which ranged from 6 to 8, indicating good quality.[17] Most studies (n = 5) examined cases under the age of 50 years,[18-22] one study examined cases under the age of 49 years,[23] one study examined cases under the age of 40 years,[24] one study examined cases among those aged 25-42 years[25] and one study examined cases in those aged 20-29 years and 30-39 years separately.[26] With respect to yCRAC outcomes evaluated, 7 studies defined any diagnosis of yCRAC to be any patient with either an adenoma or cancer.[19,21-26] Lee et al. 2019[18] included any patient with a diagnosis of a sessile serrated adenoma, thus this study is included only in the narrative synthesis and not the meta-analysis, as it is not necessarily equivalent to the criterion for yCRAC used in other studies. Six studies[19-22,24,26] assessed advanced yCRAC as outcome with 5 of these[20-22,24,26] providing a definition of an adenoma more than 10 mm in diameter or with villous or tubulovillous structure, or dysplasia or cancer. Kim et al. (2019)[19] used less a less inclusive criterion for advanced cancer, as they only considered tumors with a diameter greater than 10 mm.

Narrative Synthesis

Lifestyle risk factors evaluated included smoking in 7 studies,[18-22,24,26] and alcohol consumption in 5 studies[18,20,24,26] Smoking and alcohol consumption were established through self-report. Self-reported smoking was either dichotomous (current or past smoker vs. non-smoker)[26] or in tertiles (current smoker, past smoker, never smoker).[18-22] Alcohol consumption was determined by classifying participants as never drinkers, less than once per week, 1-2 times per week, and 2 or more times per week[18]; or as non-drinkers, non-heavy drinkers, or heavy drinkers (drinking alcohol more than 4 times per

Table 2. Characteristics of Included Studies.

Author, year	Country	Study Design	Age range (year)	Sample size	Sex, N (%) female	yCRAC outcome		Quality Score
						Any yCRAC	Advanced yCRAC	
Rosato, 2013	Italy/ Switzerland	Case control	< 45	1,690	787 (46.6%)	Any adenoma or cancer	Not examined	6
Lee, 2016	Korea	Cross-sectional	< 50	1, 776	505 (28.4%)	Any adenoma or cancer	Any one of the following: 10 mm diameter tubulovillous or villous structure high grade dysplasia	6
Kwak, 2016	Korea	Cross-sectional	20-39	4, 286	1,214 (28.3%)	Any adenoma or cancer	Any one of the following: 10 mm diameter tubulovillous or villous structure high grade dysplasia	6
Kim, 2016	Korea	Cross-sectional	<50	59,782	17,138 (28.7%)	Not examined	Any one of the following: 10 mm diameter tubulovillous or villous structure high grade dysplasia	8
Jung, 2017	Korea	Cross-sectional	30-49	57,635	16,866 (29.3%)	Cancer or adenoma	Any one of the following: 10 mm diameter tubulovillous or villous structure high grade dysplasia	7
Kim, 2018	Korea	Cross-sectional	<50	41,702	11,933 (28.6%)	Any component of villous histology, high-grade dysplasia, or carcinoma	Cancer $\geq$10 mm in diameter	8
Kim, 2019	Korea	Cross-sectional	20-29[a] 30-39[a]	72,356	Not reported	Any CRC or adenoma	Any one of the following: 10 mm diameter tubulovillous or villous structure high grade dysplasia	6
Lee, 2019	Korea	Cross-sectional	30-49	13,618	5,981 (43.9%)	Serile sessile polyp	Not examined	N/A
Liu, 2019	United States	Cohort	25-42	85,256	85,256 (100%)	Any diagnosis, self-report confirmed by medical records	Not examined	6

[a]Age groups assessed separately.

week)[19,20] or drinking more than 140 grams per week[22] or more than 20 grams per day[26] or more than 40 grams per day.[24] Finally, a single study by Rosato et al.[23] evaluated the association between consumption of certain foods and micronutrients and risk of yCRAC. For example, they report that eating a diet high in processed meats increased the risk of yCRAC (OR = 1.56, 95% CI 1.11-2.20) and a diet high in beta-carotene (OR = 0.52, 95% CI 0.37-0.72) and vitamin E (OR = 0.38, 95% CI 0.26-0.58) decreased the risk of yCRAC. However, they did not examine any lifestyle factors or clinical risk factors that allowed for comparison with other studies.

Clinical risk factors evaluated included obesity, elevated levels of blood glucose, blood pressure, and triglycerides. Obesity (defined by most studies as a BMI or body mass index equal to or greater than 25 kg/m^2) was evaluated in 6 studies,[19-22,24,26] except for one study, which defined obesity as a BMI greater than 23kg/m^2.[25] All measures, including height and weight to determine BMI, were obtained by trained health professionals. Elevated blood glucose was examined in 3 studies, and was defined as either a fasting blood glucose level of 100 mg/dL or more or prescription for glucose-lowering drugs,[19,26] or a fasting blood glucose level of 100mg/dL or more or a HbA1C level of 6.5% or more.[24] Elevated blood pressure or hypertension was defined as a blood pressure equal to or greater than 140/90mmHg[22] or a blood pressure equal to or greater than 130/85 mmHg or use of antihypertensive drugs.[24,26] Additionally, in one study, the authors did not define the criterion they used for classifying participants as having hypertension.[21] Finally, Kim et al. 2019[19] examined systolic and diastolic blood pressure separately and did not provide a criterion for elevated blood pressure. Elevated blood triglycerides was evaluated in 5 studies with 4 of these defining this factor as blood triglyceride levels at or greater than 150 mg/dL[19,22,24,26] and one study[21] not providing a clear definition. Finally, although comparatively less studied, also evaluated were chronic conditions including metabolic syndrome in 3 studies[22,24,26] and type 2 diabetes in 2 studies.

Meta-Analysis

Six studies[19,21,22,24-26] were included in the meta-analysis and we calculated pooled OR's to describe the association between the following risk factors and both any diagnosis of yCRAC and advanced yCRAC: 1) cigarette smoking, 2) alcohol consumption; 3) obesity (BMI of 25 or greater); 4) elevated blood glucose; 5) elevated blood pressure; and 6) elevated blood triglycerides . Of note, in one study by Kim et al. (2019),[26] ORs were reported separately for their 20-29 year old cohort and the 30-39 year old cohort, and as such, we separately entered corresponding ORs for each age group into relevant meta-analyses.

Lifestyle Factors (Smoking, Alcohol)

Among lifestyle factors, smoking was the most commonly evaluated risk factor in 5 studies, and all studies considered a participant a current smoker if they reported consuming cigarettes on a regular basis.[19,21,22,24,26] Three studies examined the association between smoking and any yCRAC diagnosis, and resulted in a pooled OR of 1.69 (95% CI 1.44-1.99).[22,24,26] Likewise, 4 studies examined the association between smoking and an advanced yCRAC diagnosis, and the pooled OR was 1.56 (95% CI 1.23-1.98).[19,21,22,26] Alcohol consumption was examined in 4 studies.[19,22,24,26] Researchers used different criteria to define excessive alcohol consumption including more than 20 grams per day,[26] more than 40grams per day,[24] more than 140 grams per week,[22] and consumption of more than 4 times per week.[19] Three studies examined the association between alcohol consumption and yCRAC diagnosis,[22,24,26] and the pooled OR was 1.48 (95% CI 1.40-1.57). Three studies examined the association between alcohol consumption and advanced yCRAC diagnosis,[19,22,26] and resulted in a pooled OR of 1.46 (95% CI 1.27-1.69). These results are presented in Figure 2, displaying Forest Plots for each pooled OR.

Clinical Risk Factors (Obesity, Elevated Blood Glucose, Elevated Blood Pressure, Elevated Triglycerides)

Researchers in the 6 studies included in the meta-analysis[19,21,22,24-26] also examined risk factors associated with yCRAC and advanced yCRAC that were determined by clinical measurements by trained interviewers. With respect to obesity, studies examined the association between elevated BMI and yCRAC (n = 4 studies)[22,24-26] and advanced yCRAC (n = 4 studies).[19,21,22,26] All studies applied having a BMI equal to or greater than 25 kg/m^2 as the criterion for obesity,[19,21,24,26] except for one study,[25] which used a BMI equal to or greater than 23 kg/m^2 as the obesity criterion. When we pooled the ORs, the pooled OR for obesity and any yCRAC diagnosis was 1.45 (95% CI 1.37-1.52) and the pooled OR for obesity and advanced yCRAC diagnosis was 1.26 (95% CI 1.04-1.54) (see Figure 3). When examining the association between elevated blood glucose and any yCRAC diagnosis or an advanced yCRAC diagnosis, the pooled OR for elevated blood glucose and any yCRAC diagnosis was 1.69 (95% CI 1.27-2.25) and the pooled OR for elevated blood glucose and advanced yCRAC diagnosis was 1.60 (95% CI 1.30-1.96).All studies[19,24,26] defined an elevated blood glucose level as a fasting blood glucose level at or above 100 mg/dL. Three studies evaluated elevated blood pressure and its association with any yCRAC diagnosis[22,24,26] and 3 studies evaluated the association between elevated blood pressure and an advanced yCRAC diagnosis.[21,22,26] Authors also used variable criteria for determining elevated blood pressure: (1) a systolic blood pressure of 130 mmHg or greater and/or a diastolic blood pressure of 85 mmHg or greater, or using antihypertensive drugs[24,26]; (2) a systolic blood pressure of 140 mmHg or greater and/or a diastolic blood pressure of 90 or greater[22]; or (3) the authors did not specify the criterion for elevated blood pressure.[21] When we pooled the ORs, the pooled OR for any yCRAC diagnosis was 1.56 (95% CI 1.31-1.86) and the pooled OR for an advanced yCRAC diagnosis was 1.51 (95% CI

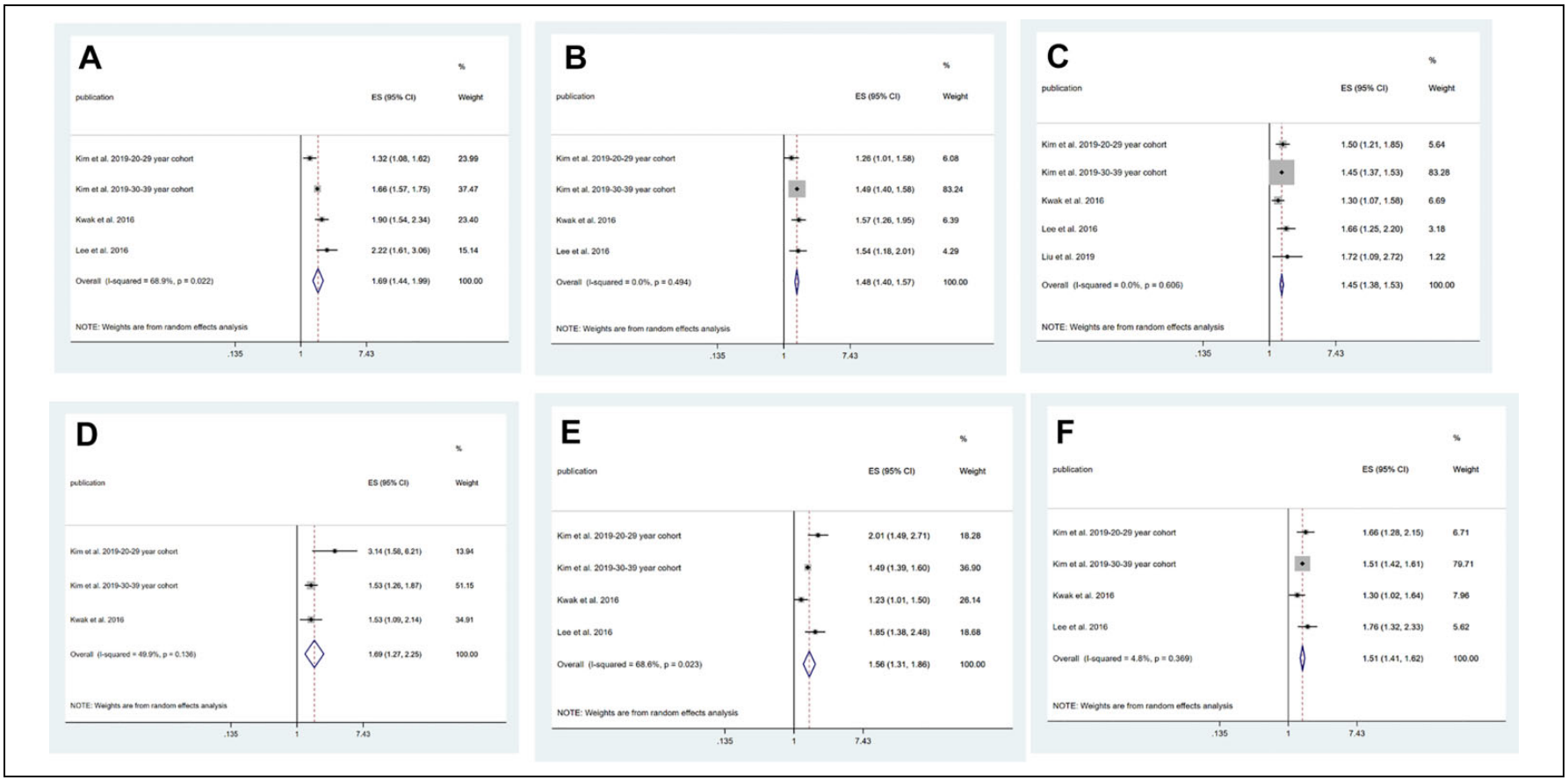

Figure 2. Pooled Odds Ratios (ORs) between lifestyle factors and clinical risk factors and any yCRAC diagnosis. 2a: smoking; 2b: alcohol consumption; 2c: obesity; 2d: elevated blood glucose; 2e: elevated blood pressure; 2f: elevated triglycerides.

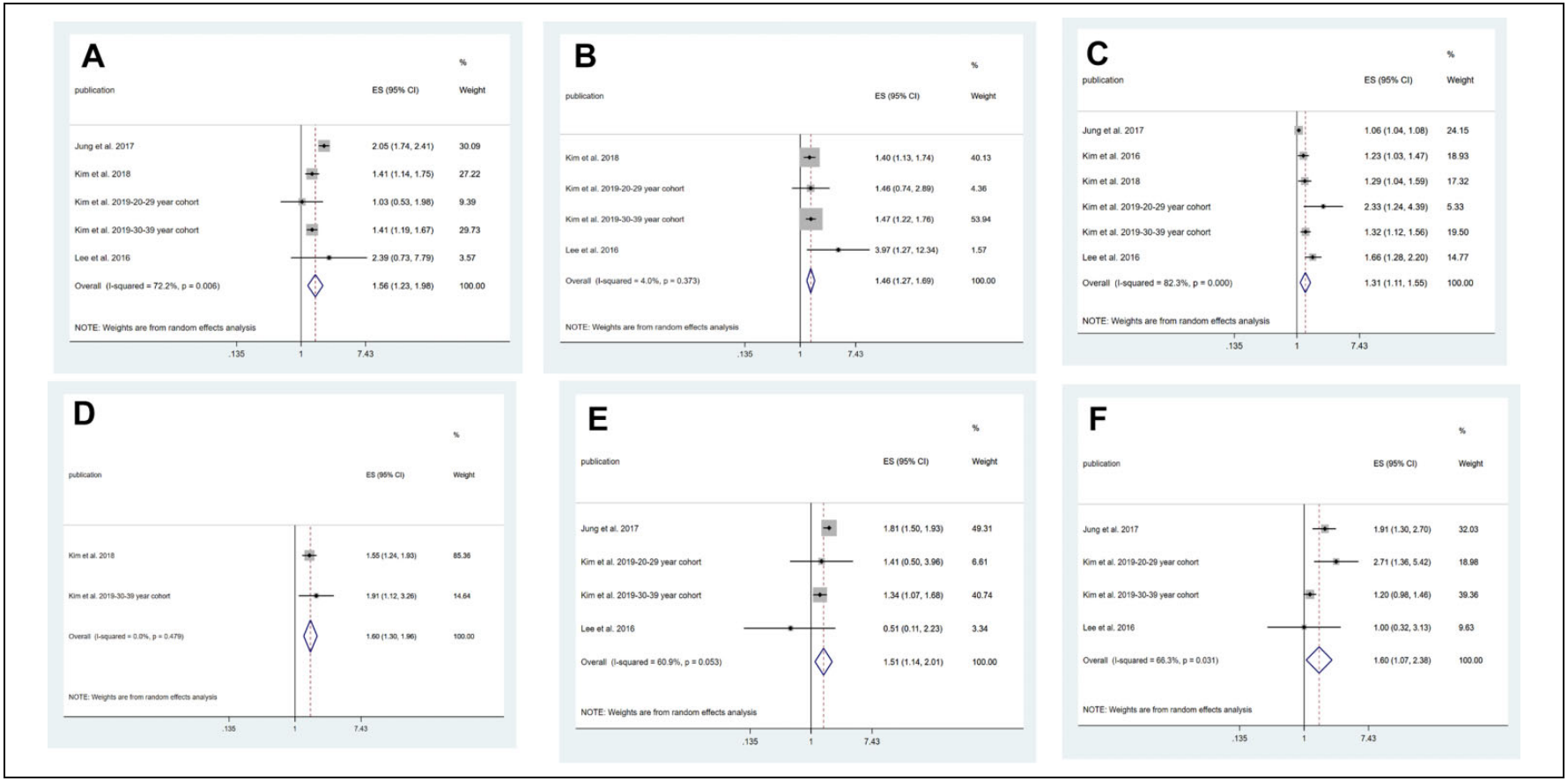

Figure 3. Pooled Odds Ratios (ORs) between lifestyle factors and clinical factors and advanced yCRAC diagnosis. 3a: smoking; 3b: alcohol consumption; 3c: obesity; 3d: elevated blood glucose level; 3e: elevated blood pressure; 3f: elevated triglycerides.

1.14-2.01).Finally, 3 studies examined the association between elevated triglycerides and any yCRAC diagnosis,[22,24,26] and 3 studies examined the association with an advanced yCRAC diagnosis.[21,22,26] The criterion for elevated triglycerides was a measured value of 150 mg/dL,[22,24,26] or the authors did not specify a minimum value.[21] The pooled OR for elevated triglycerides and any yCRAC diagnosis was 1.51 (95% CI 1.41-1.62), and the pooled OR for elevated triglycerides and an advanced yCRAC was 1.60 (95% CI 1.07-2.38).

Chronic Conditions (Type 2 Diabetes, Metabolic Syndrome)

While less frequently examined, some studies evaluated the association between clinical conditions, specifically type 2 diabetes and metabolic syndrome, and yCRAC or an advanced yCRAC diagnosis. Two studies[21,22] examined the association between type 2 diabetes and advanced yCRAC separately from a diagnosis of elevated blood glucose. Lee et al.[22] defined a diagnosis of type 2 diabetes as a fasting blood glucose of 126 mg/dL or higher or using diabetic drugs, while Jung et al.[21] did not provide a definition. The pooled OR was 1.60 (95% CI 1.32-1.95). Three studies[22,24,26] examined the association between metabolic syndrome and any diagnosis of yCRAC. Kim et al. 2019[26] used the criteria for metabolic syndrome as follows: Metabolic syndrome was diagnosed if 3 the following criteria were satisfied: (1) abdominal obesity; (2) elevated fasting blood glucose (FBG) level greater or equal to 100 mg/dL or use of glucose-lowering medications; (3) elevated blood pressure or use of antihypertensive drugs; (4) elevated triglyceride level (greater or equal fo150 mg/dL); and/or (5) reduced high-density lipoprotein cholesterol level (<40 mg/dL in men and <50 mg/dL in women). Kwak et al.[24] defined metabolic syndrome as any combination of 3 or more of the following: (1) abdominal obesity; (2) elevated blood pressure (greater than or equal to 130 mm Hg systolic blood pressure or greater than or equal to 85 mm Hg diastolic blood pressure) or receiving antihypertensive drugs; (3) elevated tryiglycerides (greater than or equal to 150 mg/dL); (4) elevated fasting plasma glucose (greater than or equal to 100 mg/dL) or receiving antidiabetic drugs; and (5) reduced HDL (40 mg/dL in men or 50 mg/dL in women). Finally, Lee et al. 2016[22] defined metabolic syndrome as the presence of $\geq$3 of the following criteria: (1) waist circumference $\geq$90 cm in men and $\geq$80 cm in women; (2) blood pressure $\geq$130/85 mmHg; (3) fasting plasma glucose $\geq$110 mg/dL; (4) triglyceride levels $\geq$150 mg/dL; and (5) HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women. The pooled OR for all 3 studies was 1.56 (95% CI 1.44-1.68).

Discussion

Our systematic review and meta-analysis has demonstrated that several modifiable lifestyle indicators, (smoking, alcohol consumption), clinical factors (obesity/elevated BMI, elevated blood glucose, elevated blood pressure, elevated triglycerides), and chronic conditions (type 2 diabetes, metabolic syndrome) are all significant predictors of both yCRAC diagnoses and advanced yCRAC diagnoses. Specifically, pooled ORs for the association between lifestyle factors of smoking (OR = 1.69, 95% CI 1.44-1.99) and alcohol consumption (OR = 1.48, 95% CI 1.40-1.57) and any yCRAC, with similar associations between these factors and an advanced yCRAC diagnosis, provide confirmatory evidence that these established risk factors for CRC[12] also play a role in the risk of yCRAC. We additionally showed associations between clinical factors and any diagnosis of yCRAC, including: obesity (OR = 1.45, 95% CI 1.37-1.52); elevated blood glucose (OR = 1.69, 95% CI 1.27-2.25); elevated blood pressure (OR = 1.56, 95% CI 1.31-1.86); and elevated triglycerides (OR = 1.51,95% CI 1.41-1.62), with similar results for the associations between clinical factors and an advanced yCRAC diagnosis. Finally, we found significant associations between yCRAC and advanced yCRAC for chronic conditions: type 2 diabetes and advanced yCRAC diagnosis (OR = 1.60, 95% CI 1.32-1.95), and metabolic syndrome and any yCRAC diagnosis (OR = 1.56, 95% CI 1.44-1.68). Thus, this systematic review provides evidence that certain lifestyle and clinical risk factors for CRC, and chronic conditions, are associated with yCRAC. Key in our review was the consideration of chronic conditions and its association with yCRAC, indicating that health professionals should be aware of conditions increasing patients' risk of yCRAC. It is important to note that some clinical factors, for example hypertension, elevated blood glucose levels, and obesity, may not automatically indicate presence of a clinically significant health condition requiring treatment. However, these factors, when present in a patient presenting with other risk factors for yCRAC, may necessitate further clinical investigation or observation.

Other researchers have also found that these risk factors are associated with CRC incidence in the general population, not specific to those under the age of 50 years. Kerr et al.[10] and Avreginos et al.[11] both found that obesity is related to CRC diagnosis in older populations, and in their review, Murphy et al.[12] report that obesity, smoking, and alcohol consumption are associated with CRC diagnoses in all age groups. One biological mechanism proposed by Avreginos et al. is that obesity is associated with a higher fat diet, microbiome alteration, and subclinical inflammation, which contributes to greater risk of developing polyps and eventually colorectal cancer. However, even with CRC in the general population, there has been less focus on the contribution of clinical risk factors (elevated blood glucose, blood pressure, and triglycerides) and chronic disease (type 2 diabetes, metabolic syndrome) to the risk and burden of CRC.

Given that the incidence and prevalence of yCRAC has been shown to be increasing in multiple countries,[27] it is important for health professionals, especially primary care providers, to be aware of the consequences of the presence of these factors in a patient, and ultimately CRC screening program recommendations[7] may need to consider revising their screening recommendations for those under the age of 50 years whose clinical risk factors and/or chronic conditions place them at increased risk of yCRAC. For example, the American Cancer Society recently lowered their recommended screening age from 50

years to 45 years, to assist in reducing the number of yCRAC cases that are not identified through routine screening.[28] Our systematic review raises the possibility that certain groups of individuals under the age at 50 years may be at increased risk of yCRAC, and thus screening programs may need to be modified to address these higher-risk groups. Additionally, there is a need for health professionals to be better aware of the possibility of yCRAC in their patients when patients present with yCRAC symptoms and investigate these cases accordingly. For example, our group recently published a patient-oriented, multi-method study indicating that yCRAC is frequently misdiagnosed in symptomatic patients under the age of 50, leading to delays in diagnosis and treatment.[29] Thus, through both modifying population-based screening programs, and educating health professionals as to the risk of yCRAC in patients under 50, especially for those in higher-risk groups identified in this systematic review, the burden of this disease in those under the age of 50 years can hopefully be reduced.

This review and meta-analysis is, to our knowledge, the first to examine risk factors for CRC specifically in those under the age of 50. While there were a limited number of published observational studies meeting study inclusion criteria, and while authors used differing criteria for both yCRAC and the risk factors for yCRAC that we examined, this study still makes a potentially important contribution given the paucity of research specific to yCRAC and the emerging nature of the field. We also collaborated with an information specialist in order to develop a comprehensive literature search across multiple databases and a detailed search strategy. We also used MOOSE reporting guidelines for our review and meta-analysis, which gives further credibility to our results.[30] There were some limitations associated with this study. First, we only searched for peer-reviewed journal articles, and may have overlooked unpublished data, such as government reports. Second, we excluded studies that examined yCRAC risk factors in those at increased risk of yCRAC, for example those individuals with genetic disorders that place them at high risk of developing CRC at an early age. This exclusion criterion was to help elucidate the associations of lifestyle and clinical factors and chronic diseases with yCRAC diagnosis. Finally, few published observational studies were available, and there is a large heterogeneity, both of the study samples and the criteria used to define both yCRAC and the risk factors in the study. However, given the emerging nature of the yCRAC research field, and the growing clinical need to address the increasing incidence of yCRAC worldwide,[27] this study still provides a potentially important contribution to the field, and can assist in developing future research in this emerging field.

Conclusions

We have demonstrated that lifestyle factors, clinical factors, and chronic conditions are all associated with yCRAC diagnosis, and warrant further attention. While some factors (i.e. smoking, alcohol consumption, obesity) may be modified through behavior change interventions, other risk factors (i.e. elevated blood glucose, blood pressure, and triglycerides) and chronic conditions (i.e. type 2 diabetes, metabolic syndrome) may be more difficult to address through these interventions. These findings suggest that there may need to be more rigorous screening by primary care providers for these risk factors, given their association with yCRAC. Eventually, populations with these elevated risk factors may ultimately require more stringent screening for colorectal cancer in individuals under age 50, in order to reduce the burden of this disease and allow for earlier treatment and better prognosis.

Abbreviations

AAPC: average annual percentage change
CRC: colorectal adenomas and cancer
OR: odds ratio
yCRAC: young-onset colorectal adenomas and cancer

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Ethics

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Supplemental Material

Supplemental material for this article is available online.

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