Annals of Gastroenterology (2025) **38,** 1-16

Early-onset colorectal cancer in patients younger than 50 years: A systematic review of the literature

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Abstract

Early-onset colorectal cancer (EO-CRC) refers to CRC diagnosed before the age of 50. Its incidence has risen in recent years, turning researchers' attention to its oncologic behavior and potentially modifiable risk factors. In this review, PubMed/MEDLINE database was searched for all original research articles concerning EO-CRC. The inclusion criteria were CRC patients under 50, without a known predisposing factor for malignancy or an inherited CRC syndrome, presenting oncological characteristics and outcomes. All studies were assessed for bias, based on the ROBINS-E 2022 tool, and were synthesized in a qualitative analysis. Twenty-nine articles, reporting on 64,376 EO-CRC patients, were included in the qualitative synthesis. Results were classified into 3 categories: a) demographics; b) histopathologic characteristics; and c) treatment outcomes. Of these publications, 21 studies agreed that rectum (45%) and left-sided (47.1%) cancers are most common in younger patients, and 5 indicated that the highest prevalence of CRC concerns the 40-49 years age group. Seventeen of 29 studies reported a higher stage (III and IV) on diagnosis, with lymphovascular and perineural invasion. Our review has some limitations: as it was based on a single database, not all studies provided information on the variables; and patients were not categorized in all studies in the same age groups, although all were under 50 years. As EO-CRC is on the rise, the need for closer monitoring and possibly earlier screening becomes apparent. Further research should focus on finding novel screening biomarkers and modifiable risk factors that would decrease mortality and improve patient outcomes.

Keywords Early-onset colorectal cancer, young adults, guidelines, 50 years old

Ann Gastroenterol 2025; 38 (XX): 1-16

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Conflict of Interest: None

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Received 11 March 2025; accepted 15 May 2025; published online 25 June 2025

DOI: https://doi.org/10.20524/aog.2025.0977

Introduction

Colorectal cancer (CRC) is listed today among the 2 most lethal cancers worldwide, with the median age at diagnosis being 68 and 72 years in males and females, respectively [1]. As 40% of CRC patients die within 5 years after their diagnosis, the first priority was to diagnose CRC at the earliest stage possible. Through thorough screening policies over the past decades, we have succeeded in decreasing CRC's mortality and achieving better results, via early detection and treatment of malignant and premalignant tumors [1,2].

In consequence, while the worldwide CRC incidence has demonstrated a steady decline of almost 1% every year, the incidence of early-onset CRC (EO-CRC) in patients younger than 50 years shows an increase of 1-2% yearly since the early 90s [2]. This accounts for almost 20,000 new cases of young CRC patients and 4000 deaths per year in that age group.

Today, we still cannot fully understand the different pathophysiological mechanisms and the diverse risk factors

that increase the risk of EO-CRC. Recent researchers have focused on further investigating EO-CRC as an almost new cancer type, highlighting that distinct genetic patterns and epigenetic changes can lead to a more aggressive and possibly lethal neoplasm [3-6]. Thus, a better understanding of the EO-CRC disease entity is more than crucial, as it would ultimately answer significant questions regarding the biological behavior of these tumors and their response to different treatment modalities.

This review deals with the current literature data on EO-CRC risk factors, histopathological characteristics and treatment outcomes. Special focus was given to the differences between young CRC patients and their older counterparts, such as the tumor location, the molecular profile and their response to systemic therapies.

Materials and methods

The PubMed/MEDLINE database was searched using the query string "colon cancer AND young adults AND 50 years" from 2004-2024. The search aimed to identify all articles on EO-CRC treatment outcomes. The research was conducted on 30th August 2024 by 2 independent researchers (IK and GK), and any selection conflict was resolved by a third researcher (GL). Data were extracted in an Excel sheet and proofread by the 2 above independent researchers; the third resolved disagreements.

Inclusion criteria for our selection included articles concerning CRC patients aged under 50 years, reporting large-scale statistics on the prevalence and incidence of EO-CRC (on at least a nationwide scale), histopathological characteristics and oncological outcomes, including the response to adjuvant and neoadjuvant treatment.

Overall, 29 articles met the criteria and were included in the qualitative synthesis. The researchers' algorithm is presented in Fig. 1.

The main variables of the review were the prevalence and incidence of EO-CRC, histopathological characteristics, such as tumor location, tumor type, microsatellite instability status (MSI), TNM stage, lymphovascular and perineural invasion, and distant metastasis, and finally treatment outcomes after curative surgery and/or systemic therapy.

The review was structured according to the PRISMA checklist, which can be found in Supplementary Table 1. All studies were assessed for bias, based on the Risk of Bias In Non-randomized Studies of Exposure (ROBINS-E 2022) tool (Table 1, and Supplementary Tables 2, 3), and were then synthesized into a qualitative analysis.

Regarding risk factors for CRC, the PubMed database was also used to identify articles focusing on EO-CRC risk factors. The authors selected the ones they thought most representative, as they provided clinical data and evidence on all the factors they proposed. Their results, as well as comments on the hypothesized mechanisms of action for each risk factor, are presented in this article.

All outcomes are presented as percentages of the whole sample for each article, while the treatment outcomes are presented in terms of overall survival (OS) and disease-free survival (DFS), using relative risk (RR) and odds ratio (OR) to assess the response to treatment.

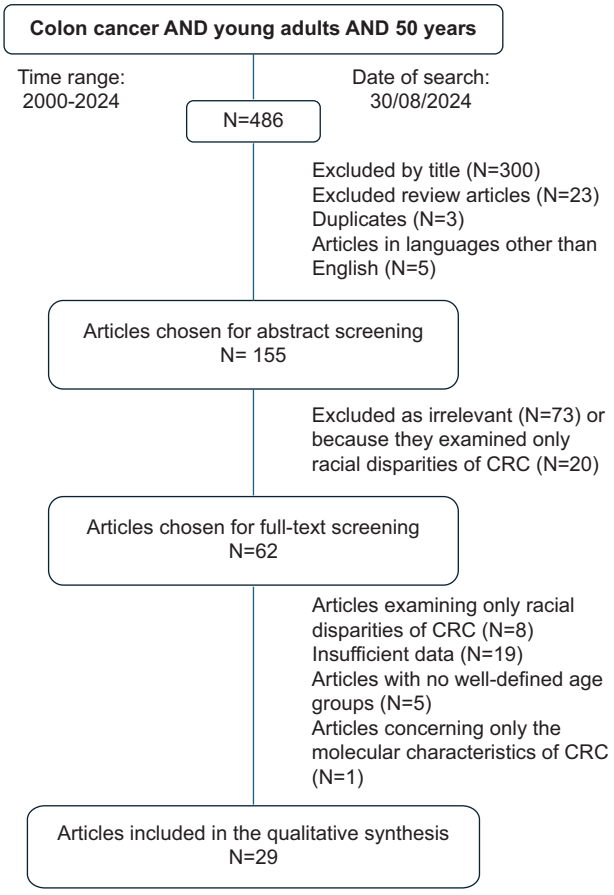

Figure 1 PubMed algorithm of search
CRC, colorectal cancer

Results

Overall, 486 articles were published during this period relating to EO-CRC. Three hundred articles were excluded as irrelevant judged by their title. Of the remaining articles, 23 were excluded as they were review articles, 3 duplicates were found, and 5 more articles were excluded as they were in languages other than English (Spanish and Portuguese).

Ninety-three more articles were excluded after the abstract screening, as 20 examined only the racial disparities of EO-CRC, without providing sufficient information about the histopathological characteristics or the treatment outcomes of the individuals included, and the rest were irrelevant to the topic of the current review, as they were merely reporting small scale statistics that could not be interpreted in the review.

Ultimately 62 articles were full-text reviewed, of which 33 were excluded because they described only racial disparities (n=8), did not provide sufficient information (n=19), did not

Table 1 Risk of bias based on the ROBINS-E-2022 tool

Study [ref.]	ROBINS-E-2022	Specific domains of risk
Siegel *et al* [2]	Low risk of bias	-
Low *et al* [3]	Some concerns	D1,2,3,4 - Low risk D5,6,7 - Some concerns
Gausman *et al* [4]	Some concerns	D1,2,6,7 - Low risk D3,4,5 - Some concerns
Teng *et al* [5]	Some concerns	D1,2,4,6,7 - Low risk D3,5 - Some concerns
Kasi *et al* [6]	Some concerns	D1,2,4,5,6,7- Low risk D3 -Some concerns
Kneuertz *et al* [7]	Low risk of bias	-
Fayaz *et al* [8]	Some concerns	D2,3,4,5,6,7 - Low risk D1 -Some concerns
Manjelievskaia *et al* [9]	Some concerns	D1,2,3,5,6,7 - Low risk D4 - Some concerns
Rodriguez *et al* [10]	Low risk of bias	-
Sifaki-Pistolla *et al* [11]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Kim *et al* [12]	High risk of bias	D1,5,6,7 - Low risk D2,3,4 - Some concerns
Park *et al* [13]	Low risk of bias	-
Loomans-Kropp *et al* [14]	Low risk of bias	-
Sanford *et al* [15]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Amri *et al* [16]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Lipsyc-Sharf *et al* [17]	High risk of bias	D1,2,3,6,7 - Low risk D4,5 - High risk
Sukhokanjanachusak *et al* [18]	Low risk of bias	-
Arhin *et al* [19]	High risk of bias	D1,3,5,6,7 - Low risk D4 - Some concerns D2 - High risk
Schellerer *et al* [20]	Low risk of bias	-
Lee *et al* [21]	High risk of bias	D1,4,6,7 - Low risk D2,3 - Some concerns D5 - high risk
Zaborowski *et al* [22]	Some concerns	D1,2,5,6,7 - Low risk D3,4 - Some concerns
Da Silva *et al* [23]	Low risk of bias	-
Myers *et al* [24]	Some concerns	D1,2,4,5,7 - Low risk D3,6 - Some concerns
Haleshappa *et al* [25]	Low risk of bias	-
Goldvaser *et al* [26]	Low risk of bias	-
Burnett-Hartman *et al* [27]	Some concerns	D1,2,3,4,7 - Low risk D5,6 - Some concerns
Dozois *et al* [28]	Low risk of bias	-
Ho *et al* [29]	High risk of bias	D4,5,6,7 - Low risk D1,2,3 - Some concerns
Yeo *et al* [30]	Low risk of bias	-

D, domain of possible bias

differentiate the age group of interest (n=5), or finally as they contained only molecular characteristics (n=1).

Finally, 29 articles were included in the synthesis, as presented in Fig. 1. All articles concerned EO-CRC, some referring to patients younger than 40 years. All articles are presented in Table 2, along with their primary and secondary outcomes.

EO-CRC demographics

Overall, 135,126 patients were included in the synthesis. Sex information was provided in 23 of the 29 studies, specifying 43,945 (52.69%) male and 39,459 (47.31%) female patients.

Siegel *et al* [2] conducted one of the biggest research projects on OECRC epidemiology in the United States, reporting that its incidence in 2020 was 17,930 new cases and that these younger patients demonstrated a mortality rate of 7%, significantly lower than the 25% seen in older patients. In a 20-year study of the incidence of CRC, whereas an overall decrease in the number of cases was observed, the incidence of EO-CRC demonstrated a rise of 1.3% annually during the study period [4]. This steady surge of EO-CRC implies a significant environmental influence on its genesis, especially as almost all researchers agreed that there was no significant genetic predisposition for cancer in the populations included [2,4,7-9,11-12].

Loomans-Kroop *et al* [14], presenting a large series of 37,138 patients, further focused on the incidence of right and left-sided colon cancers in younger patients, concluding that patients under the age of 50 more often have distal colon tumors or rectal tumors. These results are in line with those of other researchers [2,6,28], who reported that left-sided colon cancer is the most frequent type in young patients, followed by the rectum.

Moreover, the incidence of EO-CRC seems to increase with the patient's age. More specifically, Kim *et al* [12] reported a prevalence of colorectal neoplasia, in individuals undergoing colonoscopy, of 5.9% in the 20-29 years group, compared to 9.5% in the 30-39 years group. Other researchers concluded that the incidence of EO-CRC is much higher in the 40-49 years group than in younger patients [3,4,12,14], thus highlighting a need to bring forward the age of screening from 50 to 40 years.

EO-CRC histopathological characteristics

As previously stated, the majority of EO-CRC tumors are in the distal colon and rectum, even though a small increase in right-sided tumors has been noticed in the past 5 years [2]. The tumors do not demonstrate high MSI (6% for EO-CRC vs. 8% for patients aged >50 years) [4]; however, patients younger than 30 years are more likely to have tumors with high MSI compared to their older counterparts [29]. Additionally, no differences were detected concerning the *K-RAS* mutation profile [4].

Table 2 Articles about EO-CRC epidemiology and research outcomes

Study [ref.]	Year of publication	Country of study	Aim	Number of patients with EO-CRC	Primary outcome	Secondary outcomes
Siegel *et al* [2]	2020	USA	Provide colorectal cancer statistics	17,930	Colorectal cancer incidence in 2020 in the US: 147,950 and deaths: 53,200	1. 12% of new diagnosed cases of CRC in 2020 were patients <50 years old 2. Mortality was 7% for this age group vs. 25% and 68% for patients aged 50-69 and>69 years, respectively 3. During the period 2012-2016, the incidence rose by 1.8% annually for tumors in the proximal and distal colon, and rectum, and by 2.2% annually overall
Low *et al* [3]	2020	USA	Identify risk factors of CRC in young adults	651	Increasing age, smoking, and male sex were positively associated with EO-CRC	1. Obesity and aspirin use were found to be "protective" against EO-CRC 2. 575 (88%) EO-CRC patients were aged 40-49, 59 (9%) were aged 30-39, and 17 (3%) were <30 years of age
Gausman *et al* [4]	2020	USA	Identify sociodemographic and risk factors of CRC in young adults	269	Factors recognized: male sex (OR 1.87, 95%CI 1.39-2.51), inflammatory bowel disease (IBD) (3% vs. 0.4% for controls; univariable P<0.01), and family history of CRC (OR 8.61; 95%CI 4.83-15.75)	Obesity, smoking, and diabetes mellitus were not associated with EO-CRC. Mortality of EO-CRC is higher than in older patients

(*Contd...*)

Table 2 (*Continued*)

Study [ref.]	Year of publication	Country of study	Aim	Number of patients with EO-CRC	Primary outcome	Secondary outcomes
Teng *et al* [5]	2019	USA	Report oncological outcomes of patients with *de novo* EO-CRC and those with SMN (subsequent malignant neoplasm)	41,915 (2852 (6.8%) with colon SMNs)	SMNs were diagnosed at an earlier clinical and pathological T, N, and M stage (all P<0.001)	1. Patients aged <50 years demonstrated SMNs more frequently than primary tumors (83% vs. 77%; P<0.001) 2. SMN EO-CRC is found more frequently on the right colon
Kasi *et al* [6]	2019	USA	Demonstrate tumor location trends on EO-CRC	3381	Rectum is the most common sight of EO-CRC (49.8%)	1. Incidence of EO-CRC increased by 0.26% per year (P<0.001)
Kneuertz *et al* [7]	2015	USA	Describe stage-specific treatments and prognosis of EO-CRC (ages 18-49 years) vs. CRC in older individuals (ages 65-75 years)	13,102	Overtreatment of stage II did not better OS	1. Young patients were more likely to receive systemic chemotherapy in all stages of disease 2. Patients <40 years were more likely to receive multi-agent regimens (probably oxaliplatin or irinotecan based) rather than single-agent regimens
Fayaz *et al* [8]	2018	Kuwait	Report clinicopathological outcomes of patients with EO-CRC	130	Majority of patients had advanced disease and worse outcomes than older patients (compared to other studies)	
Manjelievskaia *et al* [9]	2017	USA	To investigate whether young adults with CRC are more likely to receive adjuvant chemotherapy and if this has any result on their survival	671	Young patients were 2-8 times more likely to receive postoperative systemic chemotherapy compared with older patients (n=465; 69.3%)	1. EO-CRC more frequently received multi-agent chemotherapy than older patients (group 18-49 years: OR 2.48, 95% CI 1.42-4.32) 2. No benefit in OS was observed despite the chemotherapy

(*Contd...*)

Table 2 (*Continued*)

Study [ref.]	Year of publication	Country of study	Aim	Number of patients with EO-CRC	Primary outcome	Secondary outcomes
Rodriguez *et al* [10]	2018	Canada	Describe the clinicopathological characteristics and treatment outcomes in EO-CRC	6,775	Younger patients were more likely to have advanced disease with more T3 and T4 tumors and higher numbers of lymphovascular invasion	1. EO-CRC stage III was 58% vs. 41% for those aged >60 years 2. ACT was delivered more often to EO-CRC (50% vs. 13%) for stages II & III
Sifaki-Pistolla *et al* [11]	2022	Greece	Comparison of the incidence of CRC among younger and older patients during the period 1992-2021	158		29.6% increase in CRC incidence from 2001 to 2011 in the age group 20-34 years
Kim *et al* [12]	2019	Korea	Report on the prevalence and risk factors of EO-CRC		1. Prevalence of EO-CRC was 5.9% in the 20-29 years group and 9.5% in the 30-39 years group	
Park *et al* [13]	2022	Korea	Comparison of clinicopathologic features and patient outcomes of EO-CRC and older patients.	111	EO-CRC patients were of higher stage upon diagnosis (T, N, and higher grade).	1. There were no significant differences in the 5-year OS rate (group 1, 86.9%; group 2, 78.6%; P=0.229) and 5-year DFS rate (group 1, 74.0%; group 2, 69.3%; P=0.517)
Loomans-Kropp *et al* [14]	2019	USA	Report trends in the incidence rates and clinicopathological characteristics of EO-CRC	37,138	1. Annual increase of incidence of EO-CRC was 1.3% (95%CI 0.9-1.7) between 1996-2016, while older patients showed a lower incidence of CRC	
Sanford *et al* [15]	2020	USA	Compare the survival outcomes of EO-CRC and older patients	35,411	Younger patients demonstrated worse cancer-specific survival over time (5 years post-diagnosis), even though their OS was better	

(*Contd...*)

Table 2 (*Continued*)

Study [ref.]	Year of publication	Country of study	Aim	Number of patients with EO-CRC	Primary outcome	Secondary outcomes
Amri *et al* [16]	2015	USA	Report clinicopathological outcomes of patients with EO-CRC	108	EO-CRC demonstrated higher rates of advanced disease, and worse cancer-related mortality compared to older patients	
Lipsyc-Sharf *et al* [17]	2022	USA		514	OS was worse, but not statistically significantly so, for EO-CRC than for patients aged >50 years	Progression-free survival did not differ between EO-CRC and older patients
Sukhokanjanachusak *et al* [18]	2020	Thailand	Report the clinicopathological features and outcomes of patients with EO-CRC	203	EO-CRC patients present at advanced stages, but they demonstrate no difference in OS and DFS compared to older patients	The 5-year survival for the entire population was 59.2%
Arhin *et al* [19]	2021	USA	To examine the survival benefit of surgical resection (primary and/ or metastatic) vs. palliative therapy in patients with metastatic EO-CRC	6,708	Significant OS benefit of receiving both PTR and metastasectomy (HR 0.34, 95%CI 0.31-0.37; P<0.01)	
Schellerer *et al* [20]	2012	Germany	To present the clinicopathological characteristics and survival rates in EO-CRC	244	OS was better for patients <50 years	Mucinous adenocarcinoma was less common for patients <50 years
Lee *et al* [21]	2016	Korea	Detect differences in CRC prevalence between young and older adults and describe risk factors of EO-CRC	1271	No significant difference in the prevalence of advanced CRC was detected between the age-groups 45-49 years and ≥50 years	
Zaborowski *et al* [22]	2023	Ireland	Report clinicopathological features and outcomes of EO-CRC patients	3378	OS and DFS survival for EO-CRC	Pathological response rates and the impact of neoadjuvant and adjuvant therapy on survival

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Table 2 (*Continued*)

Study [ref.]	Year of publication	Country of study	Aim	Number of patients with EO-CRC	Primary outcome	Secondary outcomes
Da Silva *et al* [23]	2020	Brazil	Report clinicopathological features and outcomes of EO-CRC patients	39	EO-CRC patients presented in advanced stages: 75% were stage III or IV	
Myers *et al* [24]	2013	USA	To present EO-CRC clinicopathological features	180	Advanced stage (3 or 4) was noted in 53%	EO-CRC patients were mainly symptomatic
Haleshappa *et al* [25]	2017	India	To present EO-CRC clinicopathological features	89	The median survival of EO-CRC was 23 months	Most patients were stage III and had poorly differentiated or undifferentiated lesions. They were also symptomatic in a vast majority
Goldvaser *et al* [26]	2016	Israel	Report clinicopathological differences between EO-CRC and older patients with CRC	110	EO-CRC presented with a more advanced disease (stage III or VI) 68.5% vs. 49.5% (P=0.001) of the older patients	Mucinous or signet ring cell adenocarcinomas were more common in the younger patients (29.8 vs. 18%, P=0.0006)
Burnett-Hartman *et al* [27]	2019	USA	Oncological outcomes of EO-CRC patients compared to those of older adults	1424	OS and DFS survival for EO-CRC were not significantly different from those of older individuals	EO-CRC were mainly high-grade tumors and with signet ring histology
Dozois *et al* [28]	2008	USA	Report site and symptoms of EO-CRC	1025	Left-sided EO-CRC is the most common variant	EO-CRCs usually are symptomatic at the time of diagnosis (86%)
Ho *et al* [29]	2000	Japan	To present EO-CRC clinicopathological features	124	The incidence of MSI increases significantly as the age at cancer diagnosis decreases	1. EO-CRC are of advanced stage at diagnosis (stage III N=49, 39.5%) 2. Germline mutations in the hMSH2 and the hMLH1 genes are associated with an increased risk of EO-CRC
Yeo *et al* [30]	2013	Singapore	Compare the prognosis of EO-CRC with that of older CRC patients	330	CSS for EO-CRC was 55.15%, not statistically significantly worse than the 61.1% of CSS for CRC of older patients	EO-CRC shows a higher incidence of mucinous and signet ring cell tumors (Group 1-20.5%, Group 2-8.2%, Group 3-6.2%, P<0.001)

EO-CRC, early-onset colorectal cancer; CRC, colorectal cancer; OR, overall survival; IBD, inflammatory bowel disease; SMN, subsequent malignant neoplasm; ACT, adjuvant chemotherapy; DFS, disease free survival; MS, microsatellite instability; hMSH2, human MutS homolog 2; hMLH1, human MutL homolog 1; CSS, cancer specific survival

There is a great deal of clinical data to suggest that EO-CRC is diagnosed in advanced stages, mostly in stage III, and that young patients present more frequently with larger tumors (T3 and T4) that have lymphovascular and/or perineural invasion, and even distant metastases [6,8,10,16,18,23,24,26]. Among the researchers, Da Silva *et al* presented the highest percentage of late-stage EO-CRC, with 75% of their EO-CRC patients being stage III or more [23]. Overall, the studies reported almost 15-25% of patients presenting with distal metastasis [8,13,18], more often in the liver, lung and other sites. Rodriguez *et al* [10] proved that more lymphatic metastases and deeper invasion of the intestinal wall were positively correlated with age, as patients under the age of 40 presented in their vast majority (88%) with T3 or T4 tumors, while 58% of them had already nodal metastasis. Park *et al* supported this observation, that EO-CRC was associated with a higher affected lymph node load, with 30.6% of patients being N2 [13].

Most of these young patients are symptomatic for more than 3 months, but because of their young age they compensate for their symptoms by self-caring, and they do not seek help until it is too late. It is very representative that, according to Siegel *et al* [2], a patient younger than 40 years is twice as likely to be diagnosed with advanced disease (stage III or IV) than his/her older equivalent.

Data also suggest that younger patients' cancers are more likely to be mucinous or signet-cell type [18,26,30], although Shelleler *et al* [20], in a series of 244 cases, suggested otherwise. Moreover, younger patients tend to have tumors of higher grade than those older than 50 years, which are more often characterized as poorly differentiated or undifferentiated [18,25]. These histopathological characteristics constitute the elements of a more aggressive tumor type and explain the higher cancer-specific mortality of younger patients. All results regarding the histopathological characteristics of EO-CRC are presented in Table 3.

EO-CRC treatment outcomes

As patients <50 years of age usually present in advanced disease stages [2,4,6-13,16,18,23-26,29], one might expect that they would have worse treatment outcomes. However, this does not seem to be the case, as younger and older patients show comparable results in terms of OS and DFS [2,9,13,18,20,27,30]. Numbers varied for OS 65-87% for the younger and 68-91% for the older patients. Another thing worth mentioning is that patients younger than 40 years demonstrated a 5-year OS of 68%, significantly better than their older counterparts (P=0.03) [6]. However, Lipsyc-Sharf *et al* [17] reported that patients <35 years old demonstrated a slightly shorter progression-free survival of 9.33 months, vs. 10.55 months in older-onset CRC individuals (P=0.68).

Overall, the cancer-specific mortality rates are higher for EO-CRC patients, notably 28.7% for patients <50 years compared to 18.4% for older patients (P=0.014), demonstrating the more aggressive tumor behavior in the younger group [15,16]. Readmission and reoperation rates, as well as perioperative mortality, were comparable for all age groups.

Finally, researchers reported that young patients were more likely to receive systemic chemotherapy, even in the setting of overtreatment. Interestingly, Manjelievskaia *et al* [9] reported that young CRC patients were 2-8 times more likely to receive adjuvant chemotherapy after surgery (almost 70% of the enrolled individuals). As both those investigators and Kneuert commented, the 18-39 years group was even more likely to receive multi-agent regimens (mainly oxaliplatin or irinotecan based), rather than single-agent regimens [7]. This excessive therapy, however, did not seem to have any benefit in terms of OS or DFS, as the treatment gain appeared to be nil for stage II (RR 0.90, 95% confidence interval [CI] 0.69-1.17), and marginal for stage III (RR 0.89, 95%CI 0.81-0.97) and stage IV (RR 0.84, 95%CI 0.79-0.90) [7,9,17,22,27].

In a study of 6708 patients, Arhin *et al* [19] reported a statistically significant OS benefit from both primary tumor resection (PTR) and metastasectomy (hazard ratio [HR] 0.34, 95%CI 0.31-0.37; P<0.001) compared to palliative therapy only. Moreover, they demonstrated that patients undergoing PTR or metastasectomy alone also had better OS compared to those undergoing palliative care (HR 0.46, 95%CI 0.43-0.49; P<0.001, and HR 0.64, 95%CI 0.55-0.76; P<0.001, respectively). Their results highlight the significance of surgery in younger patients, taking into consideration that their better overall health and lack of comorbidities may distinguish them from older ones. All results on EO-CRC treatment outcomes are presented in Table 4.

All articles were assessed for their risk of bias based on the ROBINS-E-2022 tool. Twenty-four were assessed to have a low risk of bias or minor concerns. Most risks of bias concern patient selection and the lack of control of the post-exposure interventions. More specifically, most research was retrospective, thus highlighting that some background checks of the patients regarding, for example, their genetic status may not have been accurate or may have been missing. The ratings of each article are presented in Table 1.

EO-CRC risk factors and their proposed mechanisms of actions

After looking at the increased incidence of EO-CRC, we quickly realized that most cases are diagnosed in advanced stages, as stated above. Thus, all treatment modalities can only achieve a medium survival rate. In this context, we thought it was important to address any potential (and most importantly modifiable) risk factors (Table 5).

To begin with, increasing age seems to affect CRC prevalence even in patients younger than 50 years old, with the incidence rates being higher in the 40-49 years group than those aged 30-39 years [2].

Furthermore, adopting the western diet has led to the massive consumption of processed foods, especially processed meat, which is a great source of sulfur. The sulfur microbial diet has been identified as an EO-CRC risk factor, as H_2S seems to degrade the intestinal mucosa and cause chronic inflammation. These changes create a perfect microenvironment for the genesis and development of cancer [31].

Table 3 EO-CRC histopathological characteristics

Study [ref.]	Number of patients	Commonest tumor location	Histopathological characteristics
Siegel *et al* [2]	17,930	Distal colon (25%) and rectum (37%)	Twice more likely to be diagnosed with advanced stage (> stage II)
Low *et al* [3]	651	Rectum (39.6%), followed by distal (30.3%) and proximal colon (30.1%)	
Gausman *et al* [4]	269	Left colon or rectum (75% vs. 59%, P=0.02)	1. Late-stage disease at diagnosis (Stage III/IV, 77% vs. 62% for older patients, P=0.01) 2. 80% were low-grade tumors 3. Lower prevalence of microsatellite instability than late-onset disease (6% vs. 18%, P=0.03) 4. No difference in *K-RAS* mutation profile
Teng *et al* [5]	39,063		
Kasi *et al* [6]	3381	Rectum, left-sided colon, and right colon: 49.8%, 28.8%, and 21.4%, respectively	Most patients were stage III (809, 30.4%) and IV (728, 27.4%)
Kneuertz *et al* [7]	13,102	Distal colon 7380 (56.3%) vs. proximal colon 5234 (39.9%)	1. Most EO-CRC were initially diagnosed at advanced stages: nodal or distant metastases (61.8%; 36.5% and 25.3% stage III and IV) 2. EO-CRC were more commonly categorized as poorly differentiated or undifferentiated tumors 2869 (21.9%), than in the older age group 7005 (18.9%)
Fayaz *et al* [8]	130		1. 82% of patients had T3 and T4 disease 2. 55% were N (-) and 15% were M(+) at presentation 3. Younger patients (<40 years) demonstrated grade 3 disease in a higher percentage (19% vs. 7%) compared to 41-50 years
Manjelievskaia *et al.*[9]	671	Left colon, n=257 (38.3%), followed by right colon, n=212 (31.6%)	Most EO-CRC were stage III on diagnosis, n=219 (32.6%)
Rodriguez *et al* [10]	6775		1. Patients with EO-CRC (age≤40 years) showed lymphovascular invasion in 35% vs. 27% in older patients, P=0.005 2. T3/T4 tumors were more common in younger patients (88% vs. 79%; P=0.005) 3. EO-CRC was accompanied by higher rates of lymph node-positive disease (58% vs. 41%; P<0.001)
Sifaki-Pistolla *et al* [11]	158		Younger patients presented higher percentages of diagnosis at a late stage (III and IV), P=0.03
Kim *et al* [12]	72,356		Prevalence of advanced disease was 0.6% and 0.9%, for the 20-29- and 30-39-year-old groups, respectively (P=0.005)
Park *et al* [13]	111	Left colon n=46 (41.4%) followed by rectum n=41 (36.9%) vs. Right colon n=24 (21.6%)	1. EO-CRC were mainly stage III on diagnosis, n=42 (37.8%), while older patients were mainly stage II, n=349 (34.4%) 2. EO-CRC demonstrated higher rates of T4 tumors, n=23 (20.7%) vs. n=135 (13.3%) in the older group 3. EO-CRC showed positive node disease in a higher percentage than the older group: N1 n=21 (18.9%) and N2 n=34 (30.6%) vs. N2 for the older group, n=165 (16.3%) 4. EO-CRC was poorly differentiated or undifferentiated in more cases (~5%)
Loomans-Kropp *et al* [14]	37,138	Left colon	
Sanford *et al* [15]	35,411	Distant colon	
Amri *et al* [16]	108	Left colon and sigmoid 45.5%	EO-CRC demonstrated higher rates of metastatic (20.4% vs. 8.0%; P<0.001), node-positive disease (54.6% vs. 39.4%; P=0.002), and extramural vascular invasion (38.9 vs. 29.4%; P=0.043) compared to the older group

(*Contd...*)

Table 3 (*Continued*)

Study [ref.]	Number of patients	Commonest tumor location	Histopathological characteristics
Lipsyc-Sharf *et al* [17]	514		There was no statistically significant difference in MSI status between the age groups
Sukhokanja-nachusak *et al* [18]	203	Left colon n=46 (41.4%) followed by rectum n=41 (36.9%) vs. right colon n=24 (21.6%)	1. More frequent late-stage of disease (80.7% in stage III-IV vs. 19.3% in stage I–II) 2. More commonly signet ring cell/mucinous histology than in older patients
Arhin *et al* [19]	6708	Left colon	
Schellerer *et al* [20]	244	Distant colon	Lymphatic invasion was more frequent in EO-CRC, n=103 (42.2%), as was perineural invasion, n=25 (10.2%)
Lee *et al* [21]	1271	Left colon and sigmoid 45,5%	
Zaborowski *et al* [22]	3378	Left colon n=46 (41.4%) followed by rectum n=41 (36.9%) vs. Right colon n=24 (21.6%)	1. MSI was detected in 20%, representing 10% of rectal and 27% of colon cancers. 2. Lymphovascular invasion, extramural invasion, and perineural invasion were present in 34.6%, 29.9%, and 19.4% of colon cancers and 33.0%, 22.6%, and 21.1% of rectal cancers, respectively
Da Silva *et al* [23]	39	Left colon	1. EO-CRC patients presented in advanced stages - 75% were stage III or IV 2. EO-CRC were more frequently poorly differentiated tumors (10.25% vs. 3.52%) 3. More frequent angiolymphatic invasion 36.36% and perineural invasion 42.42% vs. 211% and 19.7% for the older group, respectively
Myers *et al* [24]	180	Distant colon	Advanced stage (Stage III or IV) was noted in 53%
Haleshappa *et al* [25]	89	Left colon and sigmoid 45.5%	Most patients were stage III and had poorly differentiated or undifferentiated lesions. They were also symptomatic in the vast majority
Goldvaser *et al* [26]	110	Left colon n=46 (41.4%), followed by rectum n=41 (36.9%) vs. right colon n=24 (21.6%)	1. EO-CRC presented with a more advanced disease (stage III or VI) than the older patients, 68.5 vs. 49.5% (P=0.001). 2. EO-CRC showed a higher incidence of lymphovascular invasion (LVI) (13.8 vs. 3%, P=0.0006) and venovascular invasion (VVI) (25 vs. 13.1%, P=0.01) 3. More lymph nodes were involved in younger patients than in older ones (57.3 vs. 40.3%, P=0.006), with a mean of 7.2 and 4.6 involved lymph nodes, respectively (P=0.02) 4. Mucinous or signet ring cell adenocarcinomas were more common in the younger patients (29.8 vs. 18%, P=0.0006)
Burnett-Hartman *et al* [27]	1424	Left colon	EO-CRC were mainly high-grade tumors, and signet ring histology
Dozois *et al* [28]	1025	Distant colon	
Ho *et al* [29]	124	Left colon and sigmoid 45.5%	1. The incidence of MSI increased significantly as the age at cancer diagnosis decreased 2. EO-CRC are mainly of advanced stage at diagnosis (stage III N=49, 39.5%) 3. Germline mutations in the *hMSH2* and the *hMLH1* genes are associated with an increased risk of EO-CRC
Yeo *et al* [30]	330		1. EO-CRC shows a higher incidence of mucinous and signet ring cell tumors (Group 1 20.5%, Group 2 8.2%, Group 3 6.2%, P<0.001) 2. EO-CRC seems to be more poorly differentiated (Group 1 20.0%, Group 2 9.7%, Group 3 7.4%, P=0.014) 3. They also present a higher rate of regional lymph node metastases (Group 1 65.7%, Group 2 60.8%, Group 3 51.0%, P=0.001) and distant metastases (Group 1 31.5%, Group 2 24.1%, Group 3 19.4%, P=0.006)

EO-CRC, early-onset colorectal cancer; MSI, microsatellite instability; LVI, lymphovascular invasion; VVI, venovascular invasion; hMSH2, human MutS homolog 2; hMLH1, human MutL homolog 1

Table 4 EO-CRC treatment outcomes

Study [ref.]	Number of patients	Treatment outcomes
Siegel *et al* [2]	17,930	1. There was a steady increase in mortality by 1.3% during the period 2008-2017, BUT better 5-year relative survival rates than older patients 2. OS was almost the same for the younger and older groups
Kasi *et al* [6]	3381	The 5-year OS for patients aged <30 years was 68% (95%CI 62-74), significantly better than that of older individuals, 30-39 and 40-49 years old (P<0.003)
Kneuertz *et al* [7]	13,102	1. Young patients were more likely to receive systemic chemotherapy in all stages of the disease 2. Patients aged <40 years were more likely to receive multi-agent regimens (probably oxaliplatin or irinotecan-based) rather than single-agent regimens. 3. Treatment gain from chemotherapy on EO-CRC was nil for stage II (RR 0.90, 95%CI 0.69-1.17) and marginal for stage III (RR 0.89, 95%CI 0.81-0.97) and stage IV (RR 0.84, 95%CI 0.79-0.90)
Manjelievskaia *et al* [9]	671	1. Young patients were 2 to 8 times more likely to receive postoperative systemic chemotherapy compared with older patients (n=465; 69.3%) 2. EO-CRC more frequently received multi-agent chemotherapy than older patients (group 18-49 years: OR 2.48, 95%CI 1.42-4.32) 3. There were no statistically significant differences in OS and DFS between the young patients treated with surgery alone and those who received adjuvant chemotherapy postoperatively.
Rodriguez *et al* [10]	6775	1. ACT was delivered more often to EO-CRC (50% vs. 13%) for stages II & III 2. OS (HR 0.32, 95%CI 0.21-0.49) and CSS (HR 0.41, 95%CI 0.26-0.64) were superior for individuals aged ≤40 years
Park *et al* [13]	111	There were no significant differences in 5-year OS rate (group 1, 86.9%; group 2, 78.6%; P=0.229) and 5-year DFS rate (group 1, 74.0%; group 2, 69.3%; P=0.517)
Sanford *et al* [15]	35,411	The 5-year cancer-specific survival for stage IV EO-CRC improved from 20.3-67.7% (change=47.4%) for young adults, while for older patients the improvement was from 15.6% to 77.2% (change=61.6%)
Amri *et al* [16]	108	Cancer-related mortality was greater in the<50 years group (28.7 vs. 18.4%, P=0.011) Readmission, reoperation, and perioperative mortality rates did not differ significantly
Lipsyc-Sharf *et al* [17]	514	1. The median OS was 27.07 months in EO-CRC vs. 26.12 months in patients aged >50 years, with an adjusted HR of 0.98 (95%CI 0.88-1.10; P<0.78). 2. Patients aged <35 years had a shorter median PFS of 9.33 (95%CI 7.00 to 11.96) months vs. 10.55 (95%CI 10.12 to 10.94) months in older-onset CRC patients with adjusted HR 1.22 (95%CI 0.93 to 1.59; P-trend <0.68). 3. Fewer EO-CRC patients received prior adjuvant chemotherapy (10.9% vs. 15.3%; P<0.01) Younger patients overall received higher doses of chemotherapy and multifactorial treatment regimens
Sukhokanja-Nachusak *et al* [18]	203	1. 5-year survival for the entire population was 59.2%, and there was no difference in OS and DFS between the younger and the older group 2. Male sex (P=0.004), signet ring cell histology (P=0.022), lymphovascular invasion (P=0.005), and perineural invasion (P=0.009) were associated with worse DFS
Arhin *et al* [19]	6708	1. Statistically significant OS benefit of receiving both PTR* and metastasectomy (HR 0.34, 95%CI 0.31-0.37; P<0.001) compared to palliative therapy only 2. Undergoing PTR only and metastasectomy only were also associated with better OS (HR 0.46, 95%CI 0.43-0.49; P<0.001, and HR 0.64, 95%CI 0.55-0.76; P<0.001, respectively)
Schellerer *et al* [20]	244	1. OS for EO-rectal cancer was 88% vs. 69.5% for older adults, while for EO-CRC the numbers were 82.5% and 73.2%, respectively 2. EO-CRC patients demonstrated a significant difference in adjuvant or palliative postoperative treatment they received, especially in stage IV
Zaborowski *et al* [22]	3378	1. 5-year DFS for stage I, II and III colon cancer was 96%, 91% and 68%, respectively. 5-year DFS for stages I, II and III rectal cancer were 91%, 81% and 62% 2. Neoadjuvant chemotherapy did not improve DFS in pathological node-negative or positive rectal cancer

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Table 4 (*Continued*)

Study [ref.]	Number of patients	Treatment outcomes
Haleshappa *et al* [25]	89	1. Survival in early stages was significantly higher than in advanced stages (3 and above), 34 and 19 months (P=0.0287), in those aged >40 years compared to <40: 35 vs. 23 months (P=0.0029) 2. Female patients demonstrated a better OS than men
Burnett-Hartman *et al* [27]	1424	1. OS and DFS for EO-CRC were not significantly different from those of older individuals 2. EO-CRCs were more likely to receive adjuvant therapy within 6 months of diagnosis than late-onset patients (adjusted OR 2.84, 95%CI 2.40-3.37) 3. The risk of death from all causes, and CRC, was lower in EO-CRC than in late-onset patients (HR for death from all causes 0.66, 95%CI 0.58-0.75; HR for CRC-specific death 0.66, 95%CI 0.56-0.79)
Ho *et al* [29]	124	14 patients with EO-CRC (11.3%) developed 15 metachronous cancers
Yeo *et al* [30]	330	CSS* for EO-CRC was 55.15%, not statistically significantly worse than the 61.1% of CSS for CRC of older patients

EO-CRC, early onset colorectal cancer; PTR, primary tumor resection; ACT, adjuvant chemotherapy; OS, overall survival; RR, risk ratio; DFS, disease-free survival; HR, Hazard ratio; CSS, cancer specific survival; PFS, progression-free survival

Other risk factors associated with diet appear to be sweetened drink beverages and alcohol consumption, with the latter being the most important, as acetaldehyde has several proven genotoxic effects and leads to gut dysbiosis, where the reactive oxygen and nitrogen species injure the intestinal wall [32,37].

Inflammatory bowel disease has also been proposed to increase the risk of EO-CRC, with researchers highlighting various epigenetic changes, such as CpG island hypermethylation. This chronic inflammation is identified as an "oxyradical over-load" state, which stimulates some of the major carcinogenic pathways, such as the APC/tumor suppressor gene/CIN pathway, the MSI pathway, and the CIMP pathway [33,34]. However, genetic factors, such as somatic genetic mutations and clonal expansion noted in the IBD patients' genome, may also lead to distinct cell populations of the colon becoming more widely distributed over time and occupying wider zones of the mucosa. Consequently, some dysregulated subclones of these cells grow at the expense of the normal surrounding epithelium, resulting in a malignant environment where CRC grows and expands [34].

In this context of an altered intestinal environment, changes in the gut microbiota seem to play a crucial role in the genesis and progression of cancer, with the increase of "bad" microbes (e.g., the *Bacteroidaceae* species) at the expense of protective ones [38].

In addition, metabolic syndrome—and especially obesity—have been accused of being promoters of EO-CRC, as insulin resistance has been implicated in triggering immune cell response and promoting tumorigenesis [35,36,41].

Last but not least, smoking has been identified, by almost all researchers, as a major risk factor for CRC in young patients. Several smoke carcinogens are well-known today: nitrosamines, benzene, heterocyclic amines and polycyclic aromatic hydrocarbons. Their effects on normal DNA include CpG methylation, the cause of the *B-Raf* gene (*BRAF*) mutation, and the activation of the oncogenic MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway [40].

Discussion

EO-CRC is defined as colorectal cancer that occurs before the age of 50 years. Even though the global prevalence of CRC has tended to decrease over the last decades, EO-CRC seems to be on the rise [2,3] Interestingly, CRC is the leading cause of cancer incidence and mortality among individuals aged <50 years in America [42]. On the other side of the ocean, the incidence of EO-CRC in England has also continued to increase over the past 50 years, as Exarchakou *et al* report, with a distinct rise in cases of rectal cancer among patients younger than 50 years (the incidence was 5.2% in 1993 and had risen to 19.4% by 2014) [43].

The elevated disease risk in the generations born after 1950 is called the birth cohort effect. This phenomenon refers to the strong correlation of an outcome, such as incident CRC, with the year of birth. Currently, CRC incidence has been increasing rapidly across successive generations, particularly among millennials. A possible explanation could be epigenetic changes caused by gene–environment interactions, which result in somatic mutations and cancer generation [44]. Several other factors may also have contributed, such as the adoption of a western lifestyle, involving the consumption of processed foods and alcohol, as well as smoking [31,36,40].

EO-CRC is also more frequent in men than in women, although most researchers do not report significant differences in cancer risk between the sexes [2-4,11-12]. Socioeconomic status is also commented on in several articles, with farmers demonstrating a higher incidence than white-collar laborers, and uninsured patients having a greater risk of EO-CRC, diagnosed in an advanced stage [7,11].

What seems interesting is the reference to serum 25-hydroxivitamin D as a risk factor and a potential screening tool for EO-CRC. In a study conducted in an Asian population, Kim *et al* reported in 2023 that the HR for CRC in patients demonstrating elevated 25-hydroxivitamin D levels (>20 ng/mL) was 0.41 (95%CI 0.27-0.63), while for levels between 10 and 19 ng/mL it was 0.61 (95%CI 0.43-0.86),

Table 5 Risk factors of EO-CRC and their proposed mechanism of action

Risk factor	Association (+/-)	Proposed mechanism	Study [ref.]
Sulfur microbial diet (e.g., processed meat)	+	Promotion of inflammation and carcinogenesis of the colon bilayer, caused by fragmentation of the mucosa due to H_2S	Nguyen *et al*. 2021 [31]
Sugar-sweetened beverage	+	1. Fructose causes dysbiosis and endotoxemia, impairing the mucosal barrier function and increasing its permeability, thus promoting carcinogenesis 2. The lack of dietary compensation for SSBs results in the suppression of the feeling of satiety, promoting obesity and insulin resistance (DM II)	Hur *et al*. 2021 [32]
Inflammatory bowel disease	+	1. Germline *hMSH2* mutation 2. Allelic deletion of p53 3. Methylation of CpG islands (e.g., hypermethylation of the *hMLH1* gene, and the cell cycle inhibitor p16INK4a) 4. Chronic inflammation that promotes the activation of the main carcinogenesis pathways: the APC/tumor suppressor gene/CIN pathway, the MSI pathway, and the CIMP pathway 5. Increase of the inflammation-induced tumorigenic genes: *cyclooxygenase-2* (*COX-2*), *nitric oxide* (*NO*), *synthase-2* (NOS)-2, and the interferon-inducible gene *1– 8U*	Manninen *et al*. 2013 [33] Itzkowitz *et al*. 2004 [34]
Obesity	+	1. Increase of circulating insulin and insulin-like growth factors, sex hormones, and adipokines 2. Promotion of DNA methylation 3. Promotion of the oxidation of long-chain fatty acids, leading to an increase in the number of stem cells or stem-cell-like cells in intestinal tissues, thus resulting in tumorigenesis	Li *et al*. 2018 and 2021 [35,36]
Alcohol	+	1. Genotoxic effect of acetaldehyde 2. Tissue injury by reactive oxygen species and nitrogen species 3. Changes in folate intake (deprivation) and metabolism 4. Alcohol-induced gut dysbiosis	Jin *et al*. 2023 [37]
Microbiome	+/-	1. Higher levels of *Bacteroidaceae* and lower levels of *Lachnospiraceae* increase the risk of EO-CRC, by increasing genomic instability, apoptosis, and endoplasmic reticulum stress	Adnan *et al*. 2024 [38]
Dietary vitamin D	-	1. Inhibition of proliferation, migration, invasiveness and angiogenesis of cancerous cells 2. Increased numbers and function of intestinal immune cells	Kim *et al*. 2021 [39]
Smoking	+	1. Smoke carcinogens: nitrosamines, benzene, heterocyclic amines, and polycyclic aromatic hydrocarbons 2. Promotion of microsatellite instability and CpG methylation 3. *B-Raf* gene (*BRAF*) mutation 4. Alteration of gut microbiome 5. Activation of the oncogenic MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway	Li *et al*. 2023 [40]
Metabolic syndrome	+	1. Insulin resistance and insulin growth factor-mediated oncogenesis 2. Chronic low-grade inflammatory state by elevated cytokines (tumor necrosis factor-α, interleukin-6, and C-reactive protein) triggering immune cell response and promoting tumorigenesis 3. Dysregulation of bile acids and bile acid-microbiota crosstalk disruption	Chen *et al*. 2021 [41]

EO-CRC, early-onset CRC; DM II, diabetes mellitus II; hMSH2; human MutS homolog 2; hMLH1, human MutL homolog 1; CpG methylation, cytosine – guanine island methylation; APC, adenomatous polyposis coli gene; CIN pathway, chromosomal instability pathway; MSI pathway, microsatellite instability pathway; CIMR pathway, CpG island methylator phenotype pathway; COX-2, cyclooxygenase-2; NO, nitric oxide; NOS-2, synthase-2; oncogenic MAPK/ERK pathway, mitogen-activated protein kinases/extracellular signal-regulated kinases pathway

indicating that vitamin D might have a protective role against the appearance of CRC. Moreover, lower vitamin D levels were associated with more invasive tumors. These observations led them to suggest that vitamin D could be a useful screening biomarker of patients at risk of CRC development, as it could be measured easily [45].

These results showing the vitamin's protective role on EO-CRC are further supported by a recent meta-analysis of the risk

factors of early onset CRC [46], which demonstrated a pooled OR of 0.72 (95%CI 0.56-0.92). The patient sample in this study also included an Italian population, even though the majority of patients were again Asian.

The proposed mechanism is that of angiogenesis inhibition and suppression of cell proliferation, even though a recent experimental study in mice demonstrated that vitamin D supplementation led to increased production of *Carnobacterium maltaromaticum*, a metabolite of vitamin D, which seems to have protective action against the occurrence and progression of CRC [47].

Despite their different biological behavior, EO-CRC and common CRC do not show significant differences in OS and DFS, as described above. Younger than older patients tend to receive adjuvant chemotherapy; however, this overtreatment does not affect survival rates. Younger adults also receive a combination of chemotherapeutic drugs rather than a single agent, although this multi-agent therapy does not appear to be superior to the traditional one [7,9].

What only seems to be different among the younger and the older age groups is the time needed for the diagnosis and initiation of treatment. More specifically, according to Castelo *et al*, after the initial doctor's visit (which already is delayed for most EO-CRC patients) it takes on average 4.3 days longer to diagnose an EO-CRC, compared with a CRC in the over-50s detected on a routine screening control. However, the younger patients start their treatment 4.5 days sooner than older ones [48]. All these slight differences do not affect treatment success or survival, further underlining the need for better screening, as the goal would be to diagnose an asymptomatic young adult with CRC and not wait until he seeks medical care.

The current systematic review has some limitations. Firstly, the synthesis was based on results only found in one database (PubMed/Medline). Secondly, given the different age classifications of patients under 50 (e.g., in groups of 20-29, 30-39 and 40-49), it is not possible to draw overall conclusions with accuracy. We hope that the current presentation of the existing data will help future researchers in their research planning so that they may enhance our cumulative results.

This review has not been registered in any national or international registry. The research and the original draft were structured according to the PRISMA guidelines [49]. No funding was available for the conduct or publication of the current paper, and the authors declare no competing interests.

Concluding remarks

As the prevalence of CRC among individuals younger than 50 years increases, the need for a better understanding of its biology and response to treatment becomes more direct than ever. Young patients present in stages more advanced than older ones, thus implying that the screening program for CRC detection should change and start at an earlier age.

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Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review	P1- line 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist	P2
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge	P3, lines 78-91
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses	P3, lines 92-96
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	P3-4, lines 99-127
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	P3, lines 99-102
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	P3, lines 99-102
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	P3, lines 99-104
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	P3, lines 104-105
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect	P4, lines 113-117
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	P4, lines 121-126
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	P4, lines 118-120
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	P4, lines 127-130

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	P3-4, lines 106-100, 121-126
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used	Figure 1:
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	P4, lines 118-120
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	P4, lines 118-120
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	P4, lines 132-150, Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	P4, lines 137-142
Study characteristics	17	Cite each included study and present its characteristics	Table 1.
Risk of bias in studies	18	Present assessments of risk of bias for each included study	Table 4.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots	Tables 1,2,3
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	P7, lines 258-264, Table 4.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results	P10, lines 364-370
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	NA

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	P7, lines 258-264, Table 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	P4-7, lines 151-264
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	P9, lines 315-363
	23b	Discuss any limitations of the evidence included in the review	P10, lines 364-370
	23c	Discuss any limitations of the review processes used	P10, lines 364-370
	23d	Discuss implications of the results for practice, policy, and future research	P10, lines 364-370
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	P10, lines 371
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	P3, lines 99-102
	24c	Describe and explain any amendments to information provided at registration or in the protocol	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	P10, lines 372-373
Competing interests	26	Declare any competing interests of review authors	P10, line 373
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	P10, lines 381-382

NA, not applicable

Supplementary Table 2 Risk of bias assessment, based on the ROBINS-E-2022 tool

Study [ref.]	ROBINS-E-2022	Specific domains of risk
Siegel *et al* [2]	Low risk of bias	-
Low *et al* [3]	Some concerns	D1,2,3,4 - Low risk D5,6,7 - Some concerns
Gausman *et al* [4]	Some concerns	D1,2,6,7 - Low risk D3,4,5 - Some concerns
Teng *et al* [5]	Some concerns	D1,2,4,6,7 - Low risk D3,5 - Some concerns
Kasi *et al* [6]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Kneuertz *et al* [7]	Low risk of bias	-
Fayaz *et al* [8]	Some concerns	D2,3,4,5,6,7 - Low risk D1 - Some concerns
Manjelievskaia *et al* [9]	Some concerns	D1,2,3,5,6,7 - Low risk D4 - Some concerns
Rodriguez *et al* [10]	Low risk of bias	-
Sifaki-Pistolla *et al* [11]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Kim *et al* [12]	High risk of bias	D1,5,6,7 - Low risk D2,3,4 - Some concerns
Park *et al* [13]	Low risk of bias	-
Loomans-Kropp *et al* [14]	Low risk of bias	-
Sanford *et al* [15]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Amri *et al* [16]	Some concerns	D1,2,4,5,6,7 - Low risk D3 - Some concerns
Lipsyc-Sharf *et al* [17]	High risk of bias	D1,2,3,6,7 - Low risk D4,5 - High risk
Sukhokanjanachusak *et al* [18]	Low risk of bias	-
Arhin *et al* [19]	High risk of bias	D1,3,5,6,7 - Low risk D4 - Some concerns D2 - High risk
Schellerer *et al* [20]	Low risk of bias	-
Lee *et al* [21]	High risk of bias	D 1,4,6,7 - Low risk D2,3 - Some concerns D5 - high risk
Zaborowski *et al* [22]	Some concerns	D1,2,5,6,7 - Low risk D3,4 - Some concerns
Da Silva *et al* [23]	Low risk of bias	-
Myers *et al* [24]	Some concerns	D1,2,4,5,7 - Low risk D3,6 - Some concerns
Haleshappa *et al* [25]	Low risk of bias	-
Goldvaser *et al* [26]	Low risk of bias	-
Burnett-Hartman *et al* [27]	Some concerns	D1,2,3,4,7 - Low risk D5,6 - Some concerns
Dozois *et al* [28]	Low risk of bias	-
Ho *et al* [29]	High risk of bias	D4,5,6,7 - Low risk D1,2,3 - Some concerns
Yeo *et al* [30]	Low risk of bias	-

Supplementary Table 3 Characterization of each domain that could demonstrate bias

Domains	Risks of bias
1	Risk due to confounding
2	Risk arising from measurement of the exposure
3	Risk of selection of participants
4	Risk due to post-exposure interventions
5	Risk due to missing data
6	Risk arising from the measurement of the outcome
7	Risk of bias in selection of the reported results