Original Article

Association between family history and prognosis of patients with colorectal cancer: a systematic review and meta-analysis

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Background: A family history of colorectal cancer (CRC) increases the risk of developing CRC, and numerous studies have assessed the influence of family history on survival among CRC patients. However, the prognostic effect of a family history of CRC remains uncertain. The aim of this meta-analysis was to systematically assess the association between family history and CRC prognosis.

Methods: A comprehensive literature search was performed in the PubMed, Embase, Medline, Web of Science and Scopus databases up to October 2021, based on the Population, Intervention, Comparator, Outcomes and Study designs framework. Two reviewers independently extracted data on baseline characteristics and outcomes from the included studies. The Newcastle-Ottawa Scale was used for quality assessment of each study. Either a fixed- or a random-effects model was used to calculate the pooled hazard ratio (HR).

Results: Eighteen studies comprising 80,093 CRC patients were finally included in this meta-analysis. The Newcastle-Ottawa Scale scores of the included studies ranged from 4 to 8, and 12 studies were of high quality. A significant association between family history and improved overall survival was determined in the CRC patients (HR =0.89, 95% CI: 0.81–0.99) with significant heterogeneity (I^2=65.7%, P<0.001). This effect was found in male CRC patients (HR 0.70, 95% CI: 0.56–0.88) but not females (HR =0.77, 95% CI: 0.54–1.09). The association between family history and disease-free survival was not significant (HR =0.94, 95% CI: 0.88–1.01) (I^2=21.0%, P=0.263). However, a subgroup analysis supported the prognostic value of disease-free survival in patients with stage III CRC (pooled HR =0.78, 95% CI: 0.67–0.92).

Discussion: In conclusion, a positive family history was associated with improved overall survival in CRC patients. It was also a favorable predictor of disease-free survival in patients with stage III CRC. These findings should be interpreted with caution because of limitations related to study quality and differences in the adjusted factors across studies.

Keywords: Colorectal cancer (CRC); family history; survival; meta-analysis

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Introduction

Colorectal cancer (CRC) remains one of the most common cancers worldwide (1). It accounts for approximately 9.8% of all cancers diagnosed, with approximately 1.88 million newly diagnosed cases and 915,880 deaths annually; in 2020, CRC was responsible for 9.2% of cancer-related deaths overall (1). A family history of CRC in first-degree relatives (FDRs) increases the risk of developing CRC by 2- to 4-fold (2). Individuals with a positive family history of CRC are also at higher risk of developing colorectal adenomas (3). The association between family history and the risk of CRC has been attributed to both genetic and environmental factors.

However, evidence of the association between a family history of CRC and the survival of CRC patients is inconsistent. Some studies reported improved survival in CRC patients with a positive family history (4-6), whereas other studies found no significant association (7). For example, a study of 2960 CRC patients found that family history was significantly associated with better overall survival (HR =0.539, 95% CI: 0.330–0.881) (8). In the study of Bass *et al.*, a history of CRC in a FDR was associated with worse survival (HR =1.32, 95% CI: 1.01–1.72) (9). This difference might have been due to differences in the study design, study population, or definition of family history. Thus, to assess the association between family history and CRC survival more systematically, we performed a systematic review and meta-analysis of studies examining this relationship. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1546/rc) (10).

Methods

Literature search and study selection

The following Participants, Interventions, Comparison, Outcome and Study Design criteria were applied: (I) patients with CRC as the participants; (II) family history of CRC as the interventions (exposures); most but not all of the relevant studies defined a positive family history as having at least one first-degree relative (FDR) with CRC; (III) survival of patients with or without a family history of CRC (comparison); (IV) overall, disease-free survival and CRC-specific survival of CRC patients (outcome); and (V) cohort studies (study design). A comprehensive literature search was performed in the PubMed, Embase, Medline, Web of Science and Scopus databases up to October 2021. The following terms were used in the search procedure: ('family history' or 'aggregation' or 'familial' or 'family member' or 'first degree relative' or 'second degree relative' or 'first degree relatives' or 'second degree relatives') (in any field) AND ('colorectal cancer' or 'colon cancer' or 'rectal cancer' or 'colorectal adenocarcinoma' or 'colon adenocarcinoma' or 'rectal adenocarcinoma' or 'colorectal carcinoma' or 'colon carcinoma' or 'rectal carcinoma' or 'colorectal tumor' or 'colon tumor' or 'rectal tumor') (limited in title, abstract, or key words) AND ('survival' or 'prognosis' or 'prognostic' or 'mortality') (limited in title, abstract, or key words). References cited in the included studies and relevant reviews were also searched for potentially missed studies. The retrieved reports were carefully examined to exclude duplicate studies. The titles and abstracts of the selected articles were scanned, with the full articles subsequently reviewed to include eligible studies.

The eligibility of the studies for inclusion was evaluated independently by two investigators according to the following criteria: (I) cohort study, (II) the association between family history and CRC prognosis was evaluated, and (III) HRs and 95% CIs were reported. The exclusion criteria were as follows: (I) reviews and conference papers and (II) articles written in languages other than English. The literature search and study inclusion were performed by one author (Peiwei Li), and another author (Shuyan Li) assisted if there was any difficulty.

Data extraction

Two reviewers (Peiwei Li and Shuyan Li) extracted the data, with discrepancies resolved by discussion or by a third investigator. The following information was extracted from each study: first author, publication year, study design, country of origin, sample size, age and sex of the participants, months of follow-up, cancer type and CRC stage, family history definition, risk estimates and adjusted factors. Ratios that reflected the greatest degree of control for potential confounders were used. The Newcastle-Ottawa Scale (NOS) was used for the quality assessment of each study (11). The maximum total score in the NOS is 9, with a score of 6 or higher indicating high study quality.

Statistical analysis

Heterogeneity across individual studies was assessed by the chi-squared and I^2 tests; $P \leq 0.05$ and/or $I^2 > 75\%$ were considered to indicate significance (12). Pooled HRs and

95% CIs were calculated using a random-effects model if there was significant heterogeneity; otherwise, a fixed-effects model was applied. Most of the HRs extracted from the included studies were adjusted HRs, except for one study in which a crude HR was reported. Also, the factors age, sex, disease stage and tumor location were adjusted for in most of the analyses, as shown in *Table 1*. Other adjusted factors included body mass index, smoking, alcohol and tumor differentiation (*Table 1*). A primary meta-analysis was conducted to assess the associations of CRC family history with overall survival, disease-free survival and CRC-specific survival in CRC patients. Subgroup analyses and sensitivity analyses were then conducted to explore the sources of heterogeneity and to evaluate the potential modifying effect of factors such as definition of CRC family history, tumor location (colon or rectum), study design, country of origin, sex, sample size and CRC stage. Begg's funnel plots and Egger's test were used to explore publication bias risk. All analyses were conducted using Stata software (V.11.0; StataCorp, College Station, TX, USA). Statistical significance in all tests was defined as P<0.05.

Results

Description of the included studies

The literature search yielded 4,352 potentially eligible studies, of which 34 were potentially relevant. Sixteen studies were excluded because they did not report the association between family history and CRC survival (n=6), were not original articles (n=4), or contained insufficient data (n=6).

Finally, 18 studies comprising 80,093 CRC patients met the inclusion criteria for the meta-analysis (4-9,13-24). The selection process is presented in *Figure 1* and the characteristics of the included studies in *Table 1*. Among the included studies, 6 were prospective studies and 12 retrospective studies. Only 4 studies were conducted in Asia, while the remaining 14 were performed in Western countries. The sample size of the included studies ranged from 112 to 31,801. Most of the studies enrolled CRC patients with any disease stage, but four included only stage III CRC patients, two studies only colon cancer patients, and one study only patients with stages I-III CRC. For most of the included studies (n=13), a positive family history was defined as having at least one FDR with CRC. Other definitions of a positive family history were: at least one family member with CRC (14), parent or sibling with CRC (16) and near relatives with CRC (24). One study did not provide a definition of family history (15). The NOS scores of the included studies ranged from 4 to 8, and 12 studies were of high quality (Table S1).

Association between family history and overall survival in CRC

Seventeen studies assessed the association between family history and CRC overall survival in a total of 66,947 CRC patients. In the pooled analysis, the HR was 0.89 (95% CI: 0.81–0.99), and there was significant heterogeneity (I^2=65.7%, P<0.001) (*Figure 2*).

The results of the subgroup analyses are presented in *Table 2*. In those studies that defined a positive family history of CRC as a FDR with CRC, the pooled HR was 0.88 (95% CI: 0.80–0.97); in studies using another definition of a positive family history, the HR was 1.31 (95% CI: 0.47–3.59). The pooled HR for the association between a family history and overall survival in CRC patients was 0.70 (95% CI: 0.56–0.88) in males (*Figure 3A*) and 0.77 (95% CI: 0.54–1.09) in females (*Figure 3B*), suggesting that a family history of CRC was associated with improved overall survival in males but not in females. In terms of the CRC stage, a positive family history was associated with better overall survival in patients with stage III CRC (pooled HR =0.76, 95% CI: 0.64–0.90), while there no significant association in patients with other CRC stages. The results of subgroup analyses performed according to tumor location, geographic region, study design and sample size are shown in *Table 2*. Subgroup analyses indicated that tumor location, geographic region, sex and sample size as the sources. For example, although the pooled analysis showed the significance of the association between family history and CRC overall survival (I^2=60.5%, P=0.001), this did not apply to male patients (I^2=0%, P=0.464).

Association between family history and disease-free survival in CRC

Eight studies involving 44,129 participants evaluated the influence of family history on the disease-free survival of patients with CRC. The pooled HR was 0.94 (95% CI: 0.88–1.01), without significant heterogeneity (I^2=21.0%, P=0.263) (*Figure 4*). In the sensitivity analysis, the pooled HR was 0.88 (95% CI: 0.77–1.01) after excluding one study that did not define a positive family history as an FDR with CRC. Interestingly, family history was a favorable predictor

Table 1 Characteristics of the included studies

Author/year	Design	Country of origin	Sample size	Age (years) (mean or median)	Gender	Months of follow up	Cancer type and stage	Family history definition	Adjusted factors	Quality Score
Pesola/2020 (13)	Retrospective	Sweden	31,801	68	M/F	33.6	CRC I-IV	First-degree relatives with CRC	Age, stage	5
Parisi/2020 (14)	Retrospective	Italy	112	67	M/F	41.9	CRC III	At least one family member with CRC	None	4
Azzam/2020 (15)	Retrospective	Saudi Arabia	143	59.4	M/F	36	CRC I-IV	No clear definition	Age, gender, stage, treatment	5
Park/2019 (4)	Retrospective	Korea	979	59.7 for FH– 57.5 for FH+	M/F	115.2	CRC III	First-degree relatives with CRC	Age, gender, BMI, smoking, alcohol, T and N stage, differentiation, CEA, performance status, MSI status, adjuvant chemotherapy	5
Lee/2019 (8)	Retrospective	Korea	2,960	64.2 for FH– 62.0 for FH+	M/F	41	CRC I-IV	First-degree relatives with CRC	Age, gender, BMI, ASA, TNM stage, lympho-vascular invasion, perineural invasion, differentiation, tumor size, CEA, adjuvant chemotherapy, MSI	7
Chong/2018 (7)	Mostly prospective	USA	5,010	71 for FH– 70 for FH+	M/F	55.2	CRC I-IV	First-degree relatives with CRC	Age, sex, BMI, smoking, regular use of aspirin or NSAIDS, history of endoscopy screening, and stratified by tumor location, stage and study site	6
Lee/2017 (16)	Retrospective register based	Sweden	23,928	60	M/F	Nr	CRC I-IV	Parent or sibling with CRC	Age, gender and calendar year of diagnosis, socioeconomic status and the region where the individual was diagnosed with cancer	7
Jansson-Knodell/2017 (17)	Prospective	North America	1,935	58	M/F	81.6	CRC III	First degree relatives with CRC	Age, sex, race, performance status, T/N stage, treatment arm, BMI, histologic grade, tumor location, KRAS/BRAF mutation status, and MMR status	7
Phipps/2014 (18)	Prospective	North America and Australia	4,284	53.9 for FH– 56.8 for FH+	M/F	Nr	CRC I-IV (Nr)	First degree relatives with CRC	Sample weight, age at diagnosis, year of diagnosis, study site, sex, history of endoscopy screening, cigarette smoking history, and body mass index, tumor site and MSI status	5
Lee/2014 (19)	Retrospective	Korea	971	60.2 for FH– 56.9 for FH+	M/F	49.1	CRC III	First degree relatives with CRC	Age, gender, smoking, BMI, location of tumor, CEA level, differentiation, T and N stage	7

Table 1 (*continued*)

Table 1 (*continued*)

Author/year	Design	Country of origin	Sample size	Age (years) (mean or median)	Gender	Months of follow up	Cancer type and stage	Family history definition	Adjusted factors	Quality Score
Morris/2013 (5)	Retrospective	UK	10,782	60	M/F	Nr	CRC I-IV	First degree relatives with CRC	Age, gender, stage, tumor location	6
Birgisson/2009 (20)	Prospective	Sweden	318	73 for FH– 75 for FH+	M/F	72	CRC I-IV	First degree relatives with CRC	Age, gender, TNM stage, differentiation, and vascular invasion	6
Zell/2008 (21)	Retrospective	USA	1,154	64 for colon cancer 62 for rectal cancer	M/F	111.6	CRC I-IV	First degree relatives with CRC	Age, gender, ethnicity, tumor-node-metastasis stage, site within the colorectum, histology, treatment with surgery, radiation therapy, and chemotherapy	7
Kirchhoff/2008 (22)	Retrospective	USA	1,469	20–74	F	94.8	CRC I-IV	First degree relatives with CRC	Time period, age at diagnosis, endoscopy screening history, and smoking status, and is stratified by disease extent at diagnosis	7
Chan/2008 (6)	Prospective	USA	1,087	60 for FH– 63 for FH+	M/F	67.2	CC III	First degree relatives with CRC	Age, sex, race, performance status, depth of invasion, number of positive lymph nodes, presence of clinical perforation at the time of surgery, presence of bowel obstruction at the time of surgery, postoperative carcinoembryonic antigen, differentiation, and treatment arm	7
Bass/2008 (9)	Prospective	USA	1,001	61.8 for FH– 61.9 for FH+	F	Nr	CRC I-IV	First degree relatives with CRC	Stage of disease, histologic grade, age, BMI, smoking history, use of chemotherapy, history of prior screening endoscopy, primary tumor location, and year of diagnosis	7
Slattery/1995 (23)	Retrospective	USA	2,236	Nr	M/F	Nr	CC I-IV	First to fourth degree relatives with colon cancer	Age, gender and stage	6
Kune/1992 (24)	Retrospective	Australia	705	66	M/F	Nr	CRC I-III	Near relatives with CRC	Age, gender and site	5

CRC, colorectal cancer; Nr, not reported; FH, family history; BMI, body mass index; CEA, carcinoembryonic antigen; MSI, microsatellite instability; ASA, American Society of Anesthesiologists; NSAIDS, nonsteroidal anti-inflammatory drugs; MMR, mismatch repair.

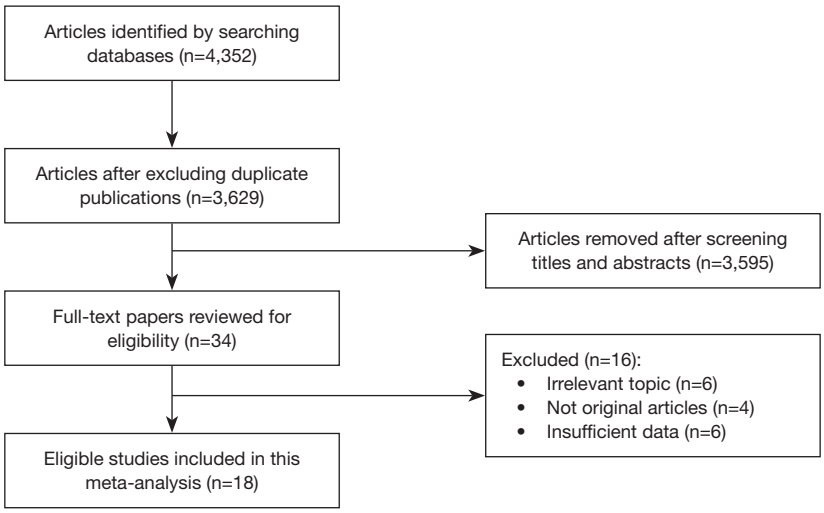

Figure 1 Flow diagram of the selection process.

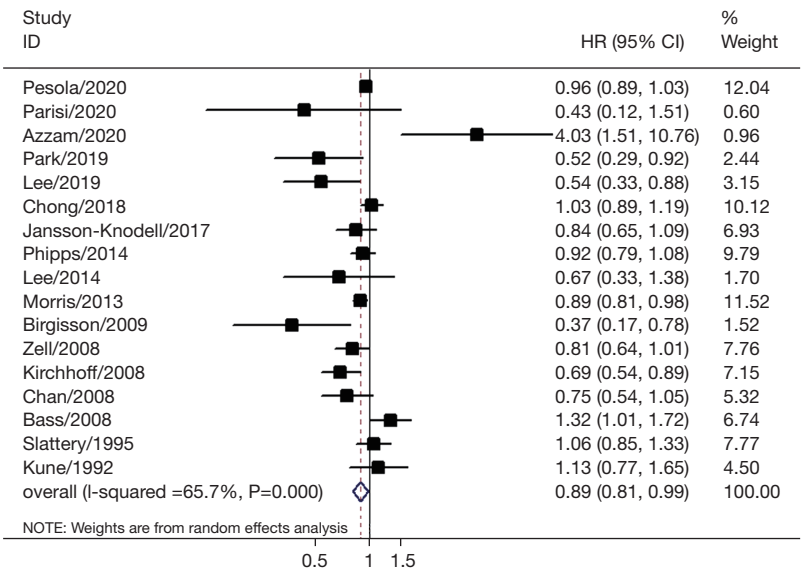

Figure 2 Forest plots for the association between family history and overall survival of CRC. CRC, colorectal cancer.

of disease-free survival among patients with stage III CRC (pooled HR =0.78, 95% CI: 0.67–0.92).

Association between family history and CRC-specific survival

Based on the results of seven studies involving 35,116 patients, there was no significant association between a family history of CRC and CRC-specific survival (pooled HR =1.00, 95% CI: 0.87–1.15).

Publication bias

Begg's funnel plots and Egger's tests suggested no evidence of publication bias in the present analyses.

Discussion

This meta-analysis was based on 18 studies evaluating the association between family history and overall survival, disease-free survival, or CRC-specific survival in CRC patients. The pooled results indicated that patients with a

Table 2 Subgroup analyses results for the association between family history and CRC overall survival

Factor	Pooled HR	95% CI	I^2 (%)	P
Tumor location				
Colon cancer	0.91	0.80–1.04	52.3	0.021
Rectal cancer	0.84	0.66–1.07	48.8	0.069
FH definition				
FDR with CRC*	0.88	0.80–0.97	63.5	0.001
Others	1.31	0.47–3.59	76.4	0.014
Stage				
I	0.54	0.28–1.04	0	0.724
II	0.67	0.41–1.09	0	0.418
III	0.76	0.64–0.90	0	0.783
IV	0.68	0.43–1.08	12.4	0.285
Gender				
Male	0.70	0.56–0.88	0	0.464
Female	0.77	0.54–1.09	78.6	<0.001
Design				
Prospective	0.92	0.77–1.10	68.4	0.007
Retrospective	0.87	0.76–0.99	66.5	0.001
Geographic region				
Asia	0.85	0.41–1.74	79.0	0.003
Western	0.92	0.84–1.00	58.2	0.004
Sample size				
Large	0.94	0.89–0.99	39.7	0.127
Small	0.83	0.64–1.08	73.9	<0.001

*, at least one FDR with CRC. FH, family history; CRC, colorectal cancer.

positive family history have a lower risk of overall mortality from CRC. This association was significant in male (HR =0.70, 95% CI: 0.56–0.88) but not female (HR =0.77, 95% CI: 0.54–1.09) patients. While there was no significant association between a family history of CRC and disease-free or CRC-specific survival, the association of a family history of CRC with improved disease-free survival in patients with stage III CRC was significant (HR =0.78, 95% CI: 0.67–0.92).

A possible reason for the association between a family history of CRC and improved overall survival is that individuals with a family history of cancer might be more aware of their lifestyle choices. As reported in previous studies, a diagnosis of cancer in family members improves health-related lifestyle behaviours, including quitting smoking and increasing physical activity, thus improving survival in CRC patients (25). Moreover, individuals with a positive family history of CRC might undergo more frequent and careful screening, resulting in earlier detection of cancer and thus improved survival. However, most of the included studies adjusted for other patient and disease characteristics associated with survival, including TNM stage. Genetic differences between CRC patients with and those without a family history might also explain the survival difference. Some studies reported that CRC patients with a positive family history have a higher rate of a microsatellite instability-high status, which may be associated with better survival (6,26). The effect of family history on the CRC prognosis is likely to be complex, influenced by both genetic and environmental factors, such that further studies are needed.

Several studies indicated that the association between family history and CRC prognosis is influenced by tumor location, with improved survival in patients with colon cancer but not rectal cancer (20,21), or only in those with rectal cancer (8,18). The differences in the clinical and molecular features of these two types of cancer (27) might account for the different prognostic effect of family history. In the current meta-analysis, there was no significant association between family history and overall survival in colon cancer or rectal cancer patients. Because of the limited number of studies (n=10 for colon cancer; n=7 for rectal cancer), no valid conclusion could be made regarding the association between tumor location and prognostic role of family history on CRC. Our study found that the effect of family history on CRC survival was significant in male but not in female patients. Sex-based differences in competing risks, such as cardiac disease, pulmonary disease and diabetes mellitus, might explain this finding (21). Other possible reasons are differences in the lifestyle choices between males and females with a positive family history and in the treatment of male versus female patients, such as those requiring surgery for rectal cancer.

Regarding the definition of family history, most of the included studies defined family history as 'family history of CRC in a first-degree relative'. Other definitions were 'at least one family member with a history of CRC' and 'near relatives with CRC'. The results of the included studies were pooled before sensitivity analyses were performed; studies that did not use 'CRC in a first-degree relative'

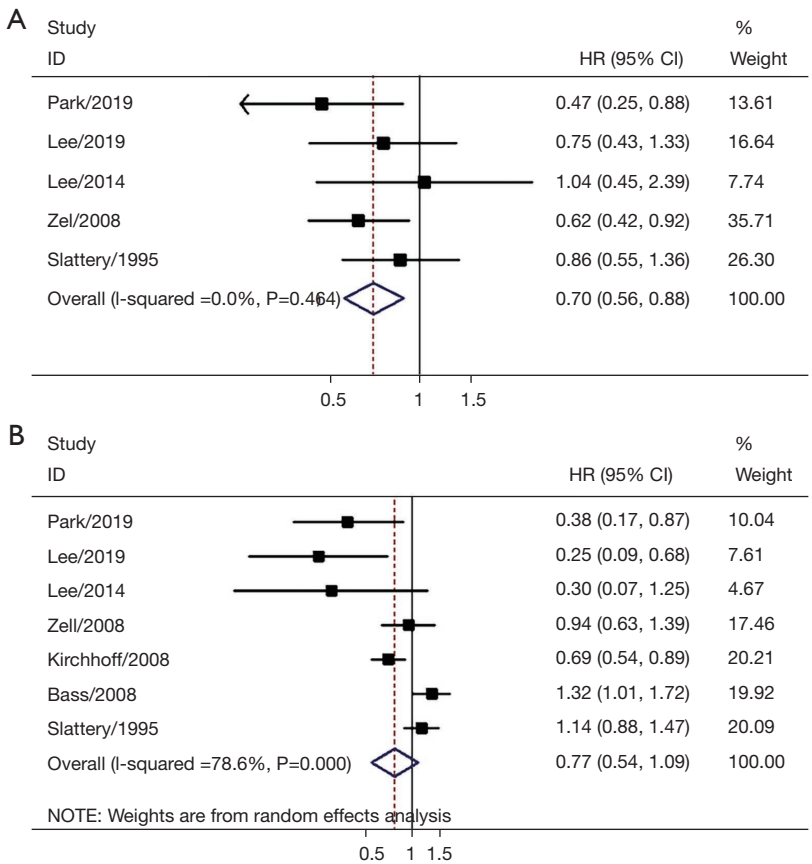

Figure 3 Subgroup analyses for the association between family history and overall survival of CRC. (A) Association between family history and survival of male CRC patients. (B) Association between family history and survival of female CRC patients. CRC, colorectal cancer.

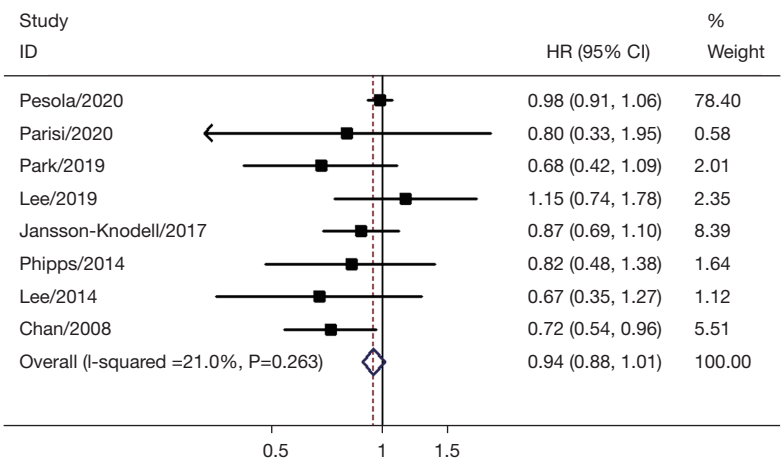

Figure 4 Forest plots for the association between family history and disease-free survival of CRC. CRC, colorectal cancer.

as the definition of family history were excluded. The similarity of the pooled results indicated that the definition of family history was not a source of heterogeneity; rather, subgroup analyses pointed to tumor location, geographic region, sex and sample size as the sources.

Our systematic review and meta-analysis comprehensively assessed observational data on the survival effect of family history on CRC patients. The pooled results indicated that a positive family history improved overall survival in this population. However, this study also had several limitations. First, the number of studies included in this meta-analysis was small, which may have affected the reliability of some of the subgroup analyses. Second, the included studies were limited to Asia, Europe, America and Australia. Third, the reasons for the heterogeneity could not be fully explained. Fourth, one-third of the included studies (n=6) were of low quality, which may have compromised the pooled results. Fifth, the confounders in each study were not always the same, which might have caused bias in the risk estimates. Finally, most of the included studies were retrospective and were thus vulnerable to bias and confounding effects.

In conclusion, this systematic review and meta-analysis found that a positive family history of CRC was associated with improved overall survival in CRC patients. The prognostic effect of a family history was affected by sex and tumor stage. A family history was also a favorable predictor of disease-free survival among patients with stage III CRC. Further studies are warranted to explore the underlying mechanisms.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1546/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1546/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Quality assessment using Newcastle-Ottawa Scale for the included studies

Author/Year	Selection				Comparability		Outcome			Total Quality Score
	Representativeness of Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment Of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Adjust for age	Adjust for 3 or more important confounders	Assessment of outcome	Follow-up Length≥ 3 years	Loss to follow-up rate≤ 30%	
Pesola/2020 (13)	1	1	0	1	1	0	0	0	1	5
Parisi/2020 (14)	0	1	0	1	0	0	0	1	1	4
Azzam/2020 (24)	0	1	0	1	1	1	0	1	0	5
Park/2019 (4)	0	1	0	1	1	1	0	1	0	5
Lee/2019 (8)	0	1	1	1	1	1	1	1	0	7
Chong/2018 (7)	1	1	0	1	1	1	0	1	0	6
Lee/2017 (15)	1	1	1	1	1	0	1	0	1	7
Jansson-Knodell/2017 (16)	1	1	1	1	1	1	0	1	0	7
Phipps/2014 (17)	1	1	0	1	1	1	0	0	0	5
Lee/2014 (18)	0	1	1	1	1	1	0	1	1	7
Morris/2013 (5)	1	1	0	1	1	1	0	0	1	6
Birgisson/2009 (19)	0	1	1	1	1	1	0	1	0	6
Zell/2008 (20)	1	1	1	1	1	1	0	1	0	7
Kirchhoff/2008 (21)	0	1	1	1	1	1	1	1	0	7
Chan/2008 (6)	0	1	1	1	1	1	1	1	0	7
Bass/2008 (9)	0	1	1	1	1	1	1	0	1	7
Slattery/1995 (22)	1	1	1	1	1	1	0	0	0	6
Kune/1992 (23)	1	1	0	1	1	1	0	0	0	5

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