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Relationship between serum lipid level and colorectal cancer: a systemic review and meta-analysis

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ABSTRACT

Objective Investigative studies report contradictory results of the relationship between serum lipid levels and the risk of colorectal cancer (CRC). We conducted a meta-analysis of prospective published studies to clarify the relationship between serum lipid and CRC risk.

Design Systematic review and meta-analysis.

Data Sources PubMed and Embase from inception until December 2020.

Eligibility criteria We considered prospective cohort and case–control studies that evaluated differences in serum lipid levels with the risk of developing CRC.

Data extraction and synthesis Two independent reviewers screened and included the studies using standardised electronic data extraction forms. The relative risks of the studies were combined with random-effect and fixed-effect models and were analysed for heterogeneity, publication bias and sensitivity.

Results Twenty-four prospective studies, including 4 224 317 individuals with 29 499 CRC cases, were included in the meta-analysis. The total pooled risk ratio (RR) for high vs low concentrations of triglyceride (TG) concentrations was reported at 1.21 (95% CI 1.09 to 1.34; I^2=46.8%), total cholesterol (TC) was at 1.15 (95% CI 1.08 to 1.22; I^2=36.8%), high-density lipoprotein cholesterol (HDL-C) was 0.86 (95% CI 0.77 to 0.97; I^2=28.8%) and low-density lipoprotein cholesterol (LDL-C) was observed at 1.03 (95% CI 0.75 to 1.41; I^2=69.4%).

Conclusions This meta-analysis shows that high levels of serum TG and TC are positively correlated with the incidence rate of CRC, while high levels of serum HDL-C are negatively correlated with CRC incidence rate. Furthermore, no association was found between LDL-C and the risk of developing CRC. Nevertheless, the heterogeneity brought about by comparative methods, demographic differences and pathological differences between the research subjects limits the effectiveness of the overall pooled results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strengths of this research are its comprehensive, prospective design, large sample size and long follow-up time.
⇒ The final result of this study is supported by high-quality studies and a thorough sensitivity analysis.
⇒ The significant heterogeneity still exists in the study results, which may limit the effectiveness of the overall pooled results.
⇒ Comparing the highest reading of the serum lipid group with the lowest group would produce different estimates, creating heterogeneity.
⇒ Demographic differences and pathological differences in cancer may have caused significant heterogeneity.

INTRODUCTION

Colorectal cancer (CRC) has a high incidence rate, a high mortality rate, rapid progress and uncomplicated metastasis, which poses a significant threat to public health.[1] Evidence shows that lipid imbalance is one of the main risk factors for CRC through associations with inflammation, oxidative stress and insulin resistance.[2] Therefore, exploring the relationship between the lipid profile and the risk of CRC is key to understanding the occurrence of CRC. As lipid profiling is convenient, the approach carries an advantage in studying its relationship to CRC.

Blood lipids are the general term used for neutral fats (triglycerides, TG) and lipids (phospholipids, glycolipids and sterols) in plasma.[3] The lipid profile includes TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).[4 5] Past studies have shown that serum lipids were closely related to cardiovascular diseases.[6] In recent years, evidence shows that plasma lipid levels may be closely related to the occurrence and development of cancer[7] and thus can be used to evaluate cancer prognosis.[8] However, the relationship between lipid profile and CRC has been inconsistent.[9 10] For example, some studies[11–15] have found an increased risk of CRC in subjects with high serum TG, while others[16–23] report contrary or insignificant associations. Similar trends were found for subjects with high TC, where an increased risk of CRC was observed,[15 18 24–27] while other studies found contrary or insignificant associations.

In addition, studies on the association between HDL-C and the risk of CRC are also contradictory.[11 12 14 16–20 23 28 29] The relationship between LDL-C and the risks associated with CRC has not been confirmed due to few studies.[11 18 19 23 29] Two meta-analyses of lipid composition and risk of CRC were published in 2014 and 2015. One of the studies showed that elevated serum TG and TC levels are associated with an increased risk of CRC.[30] While others showed that high levels of serum TG, TC and LDL-C were positively associated with colorectal adenoma but not with CRC.[31] The possible reason for the difference is that the latter included prospective studies while the other included retrospective studies.

In the current meta-analysis, more recent studies were included to further evaluate the unclear relationship between serum lipid levels and CRC. A systematic review was conducted with a meta-analysis of all prospective studies related to lipid components to explore the relationship between serum lipid and CRC risk.

MATERIALS AND METHODS

Search strategy

Systematic review and meta-analysis were performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[32] Two independent reviewers searched PubMed and Embase databases for all literature from inception to December 2020. The keywords included 'serum lipids', 'triglycerides, TG', 'total cholesterol, TC', 'high-density lipoprotein cholesterol, HDL-C, or 'low-density lipoprotein cholesterol, LDL-C' combined with 'colorectal cancer, CRC'. The detailed search strategy is shown in online supplemental table S1.

All references in the selected articles were manually reviewed to ensure that more published studies were found. The two researchers also screened the reference list for review articles and further searched the articles for other eligible studies. The search results were limited to studies published in English.

Study selection

Studies that met the following criteria were included in the meta-analysis: (1) prospective research; (2) study subjects were adults (older than 18 years); (3) serum TG, TC, HDL-C, or LDL-C concentrations were parameters of interest; (4) colorectal, colon or rectal cancer incidence were the outcome of interest and (5) reported the risk ratio (RR) or the HR with estimates of their corresponding 95% CI. Two reviewers (ZY and HT) independently evaluated potentially eligible studies using the above inclusion criteria. Twenty-four potential prospective studies from 5143 articles were identified (figure 1). If there were multiple articles in the same study population, articles with a larger sample size were selected.

Data extraction

The following information was extracted from each study: first author's name, publication year, geographic location, study design, sample size, study participants' age range, follow-up years, colonoscopy examination at the time of diagnosis, study specific-adjusted estimates with their 95% CIs for the highest versus lowest concentrations, and factors matched by or adjusted for the design or data

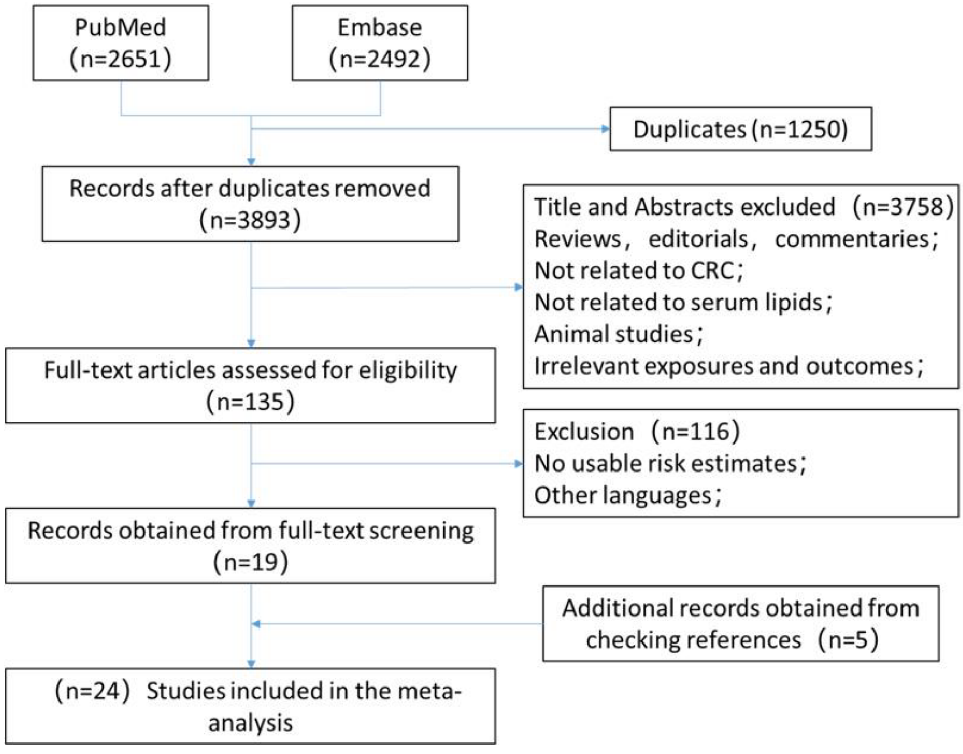

Figure 1 Flow diagram of the literature search and trials selection process. CRC, colorectal cancer.

analysis. Data from each eligible study were extracted by two independent reviewers (ZY and HT), with disagreements resolved with a majority vote by all coresearchers. When a study provides multiple risk estimates, risk estimates that reflect the maximum control degree of potential confounding factors were extracted.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to separately assess the quality of each study by both reviewers. The scores of eight or more, five to seven, and lower than five were considered high-quality, medium-quality and low-quality research, respectively.

Statistical analysis

Statistical analyses were performed using the Stata software (V.14.2). The risk estimates were extracted from each study, and the summary RRs and 95% CIs for the highest vs lowest concentrations of the selected parameters were calculated according to different heterogeneity. For undetected heterogeneity, the fixed-effect or random-effect models were used when significant heterogeneity was detected. In studies that did not use the lowest concentration class as a reference, RR was calculated according to the method provided by Hamling *et al*.[30 33] Additionally, I^2 statistics were used to represent the heterogeneity of studies. I^2 values of <30%, 30%–50% and >50% represent no heterogeneity, moderate heterogeneity and high heterogeneity, respectively. The heterogeneity between subgroups was evaluated by meta-regression, and p<0.05 indicated statistically significant results. Publication bias was analysed using Egger's or Begg's test, and p<0.05 indicated significant publication bias. Sensitivity analysis was used to analyse the stability and heterogeneity of the research results.

Patient and public involvement

This is a meta-analysis based on the evidence in the academic literature, and there is no direct participation of patients or the public in the design, implementation and reporting of this research.

RESULTS

Study characteristics

A total of 5143 studies were obtained after the search using the above keywords. Of these, 1250 publications were excluded due to duplication. The remaining 3893 studies were further evaluated according to their abstracts and titles, and 135 were screened out. Through intensive reading of the full text, studies not associated with serum lipids and the risk of CRC and having repeated research data were excluded. In addition, five studies were manually added after reading the relevant literature. Finally, 24 prospective studies that met the inclusion criteria, published between 1986 and 2019, and involved 4 224 317 individuals with 29,499 CRC events were included. Eight studies were conducted in North America,[11 20–23 34–36] 11 in Europe[12 13 15 17–19 24 27–29 37] and 5 in Asia.[14 16 25 26 38] The median duration of follow-up was 12.9 years. Characteristics of these studies are summarised in online supplemental table S2.

Quality assessment

NOS scores of the 24 prospective studies are shown in online supplemental table S3. Most studies scored 8 or 9, representing 79.2% (19 of 24) of all studies, while the lowest score was 5. Inadequate adjustment of potential confounding factors is the most common problem in low-quality studies, followed by the integrity and duration of follow-up.

Serum TG

Thirteen studies reported serum TG (nine cohort studies, two nested case–control studies and two case–cohort studies). These reports were published between 1997 and 2019 and involved 11 023 CRC cases (online supplemental table S2). Five studies were conducted in North America, six in Europe and two in Asia. The results of 13 studies showed that serum TG had a significant association with the risk of CRC (RR 1.21; 95% CI 1.09 to 1.34), with evidence of moderate heterogeneity (p=0.007, I^2= 46.8%; table 1; figure 2). The Egger's (p=0.834) and Begg's test (p=0.413) showed no evidence of publication bias, and no asymmetry was observed in funnel plots with visual inspection.

Serum TC

Fifteen studies reported serum TC (11 cohort studies, 2 nested case–control studies and 2 case-cohort studies) published between 1986 and 2017. These studies involved a total of 20 454 CRC cases (online supplemental table S2).[11 15 17–19 24–28 34–38] Four studies were conducted in North America,[11 34–36] eight in Europe[15 17–19 24 27 28 37] and three in Asia.[25 26 38] Results from 16 studies showed that serum TC was significantly associated with risk of CRC (RR 1.15; 95% CI 1.08 to 1.22), with evidence of moderate heterogeneity (p=0.017, I^2=36.8%; online supplemental table S4; figure 3). The Egger's (p=0.611) and Begg's test (p=0.560) showed no evidence of publication bias, and no asymmetry was observed in the funnel plots when visually inspected.

Serum HDL cholesterol

Eleven studies reported serum HDL-C (eight cohort studies, one nested case–control study and two case-cohort studies) published between 1997 and 2019 and involved 5869 CRC cases (online supplemental table S2).[11 12 14 16–20 23 28 29] Three studies were conducted in North America,[11 20 23] six in Europe[12 17–19 28 29] and two in Asia.[14 16] Results from these 11 studies showed that serum HDL-C had a significant association with CRC risk (RR 0.86; 95% CI 0.77 to 0.97), with evidence of little heterogeneity (p=0.117, I^2=28.8%; online supplemental table S5; figure 4). The Egger's (p=0.252) and Begg's tests (p=0.124) showed no evidence of publication bias, and

Table 1 Subgroup analysis of the correlation between serum triglyceride concentrations and colorectal cancer risk

	No of studies	Summary RR (95% CIs)	I^2 value (%)	P_h*	P_h†
Overall					
Colorectal cancer	13	1.21 (1.09 to 1.34)	46.8	0.007	
Colon cancer	4	1.29 (0.98 to 1.70)	68.5	0.007	
Rectal cancer	4	1.02 (0.76 to 1.37)	42.5	0.122	
Subgroup analyses					
Study quality					0.801
Medium	3	1.24 (0.97 to 1.58)	52.1	0.100	
High	10	1.20 (1.07 to 1.34)	45.7	0.016	
No of cases					0.311
<338	7	1.12 (0.89 to 1.41)	54.0	0.017	
≥338	6	1.24 (1.11 to 1.38)	43.4	0.053	
Follow-up years					0.682
<13	7	1.15 (0.97 to 1.37)	55.1	0.007	
≥13	6	1.24 (1.09 to 1.40)	35.4	0.135	
Geographical location					0.303
North America	5	1.13 (0.88 to 1.45)	51.1	0.069	
Europe	6	1.29 (1.15 to 1.45)	37.3	0.093	
Asia	2	0.98 (0.69 to 1.40)	65.3	0.021	
Gender					0.533
Male	5	1.32 (1.04 to 1.66)	63.9	0.007	
Female	5	1.19 (0.97 to 1.47)	41.0	0.118	
Adjustment for confounders					
Body mass index					0.347
Yes	7	1.26 (1.10 to 1.44)	42.1	0.054	
No	6	1.12 (0.94 to 1.34)	56.3	0.015	
Alcohol drinking					0.196
Yes	9	1.14 (1.02 to 1.29)	32.1	0.112	
No	4	1.31 (1.10 to 1.55)	51.2	0.045	
Cigarette smoking					0.801
Yes	10	1.20 (1.07 to 1.34)	45.7	0.016	
No	3	1.24 (0.97 to 1.58)	52.1	0.100	
Physical activity					0.654
Yes	7	1.15 (1.07 to 1.25)	0	0.496	
No	6	1.17 (1.00 to 1.36)	60.6	0.002	
Dietary factors					0.346
Yes	4	1.36 (1.10 to 1.68)	0	0.551	
No	9	1.17 (1.05 to 1.32)	55.0	0.003	
Two aforementioned confounders					0.801
Yes	10	1.20 (1.07 to 1.34)	45.7	0.016	
No	3	1.24 (0.97 to 1.58)	52.1	0.100	
Three aforementioned confounders					0.347
Yes	8	1.15 (1.00 to 1.32)	36.9	0.081	
No	5	1.28 (1.09 to 1.49)	51.0	0.038	

*P value for heterogeneity within each subgroup.
†P value for heterogeneity between subgroups with meta-regression analysis.
RR, relative risk.

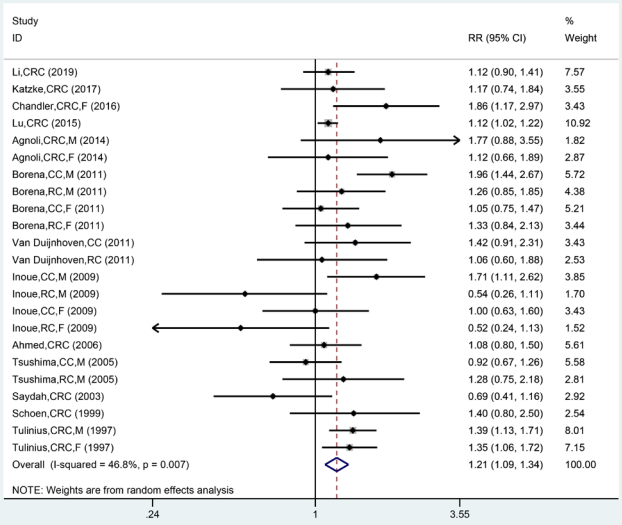

Figure 2 Forest plots on the association between serum triglyceride concentrations and colorectal cancer risk. RR, risk ratio.

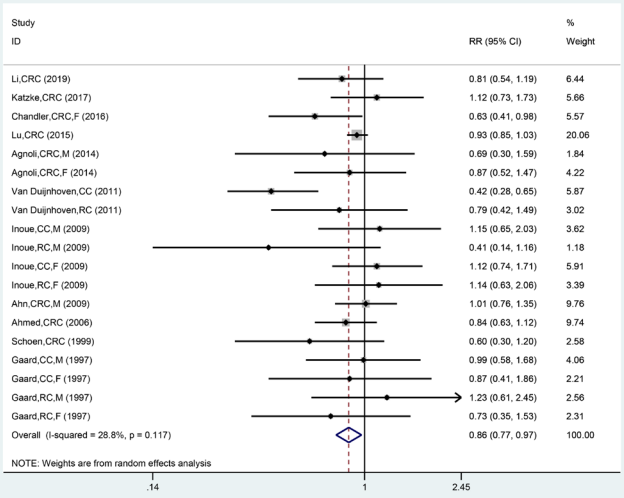

Figure 4 Forest plots on the association between high-density lipoprotein cholesterol concentrations and colorectal cancer risk. RR, risk ratio.

no asymmetry was observed in the funnel plots when visually inspected.

Serum LDL cholesterol

Five studies reported serum LDL-C (three cohort studies, one nested case–control study and one case-cohort study). These reports were published between 1997 and 2016 and involved a total of 2,162 CRC cases (online supplemental table S2).[11 18 19 23 29] Two studies were conducted in North America[11 23] and three in Europe.[18 19 29] The association of serum LDL-C with CRC risk was not observed (RR 1.03; 95% CI 0.75 to 1.41). A random-effects model was constructed due to statistically high heterogeneity among the studies (p=0.001, I^2=69.4%; online supplemental table S6; online supplemental figure 1). The Egger's (p=0.343) and Begg's test (p=0.474) showed no evidence of publication bias, and no asymmetry was observed in the funnel plots when visually inspected.

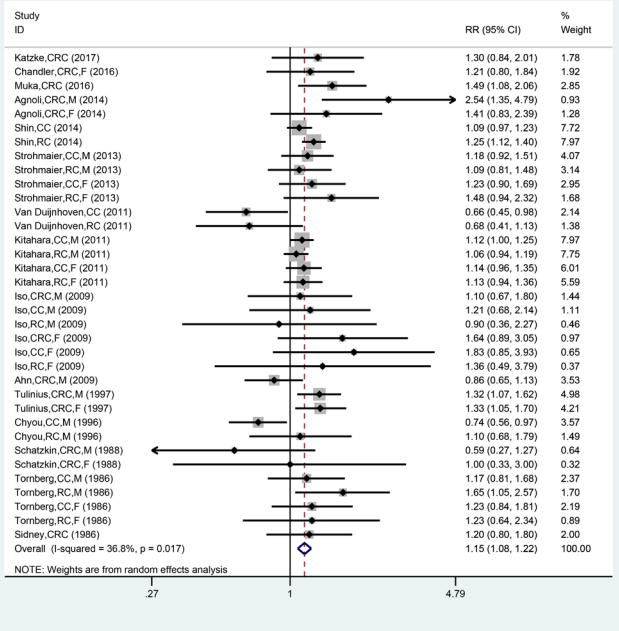

Figure 3 Forest plots on the association between serum total cholesterol concentrations and colorectal cancer risk. RR, risk ratio.

Subgroup analysis

To explore the source of heterogeneity, several preplanned subgroup analyses were conducted on the studies' characteristics. For study quality, a significant correlation was observed between TG and CRC risks in high-quality studies (RR 1.20; 95% CI 1.07 to 1.34). A similar correlation was found in high-quality studies with TC (RR 1.14; 95% CI: 1.06 to 1.21) and HDL-C (RR 0.87; 95% CI 0.77 to 0.98). A significant correlation was also observed between TG and CRC in the subgroups within the studies with the number of cases ≥338 (RR 1.24; 95% CI 1.11 to 1.38). In subgroups with follow-up at ≥13 years, higher TG levels increased the risk of CRC (RR 1.24; 95% CI 1.09 to 1.40). Furthermore, the RR for the association between TC and CRC risks was similar in Europe (RR 1.20; 95% CI 1.06 to 1.36) and Asia (RR 1.14; 95% CI 1.08 to 1.20). A significant correlation was also found between TG and CRC risks in the European subgroup (RR 1.29; 95% CI 1.15 to 1.45). However, an opposite trend was observed between HDL-C and CRC risks in the North American subgroup (RR 0.75; 95% CI 0.60 to 0.94). Furthermore, TG (RR 1.32; 95% CI 1.04 to 1.66) was associated with a higher risk of CRC in male patients, while TC (RR 1.22; 95% CI 1.11 to 1.34) or LDL-C (RR 1.33; 95% CI 1.01 to 1.76) levels were associated with a higher risk of CRC in female patients.

Sensitivity analyses

Sensitivity analyses were performed to explore the combined effect and heterogeneity among serum lipid levels and CRC studies. After studies related to TG were individually excluded, the combined effect quantity trend remained prior to exclusion. This indicates a good stability of the analysed data. A considerable part of the heterogeneity was determined to be accounted for in one study.[14] Exclusion of the study resulted in moderate heterogeneity (p=0.046, I^2=38.3%), and the RR for CRC was 1.23 (95% CI 1.12 to 1.36).

Additionally, studies that involved TC demonstrated the stability of results. Most of the heterogeneity was accounted for in three studies,[18 19 34] which reported the association between TC and CRC. After excluding these three studies, heterogeneity was nil (p=0.609, I^2=0.0%) and the RR for CRC was 1.16 (95% CI 1.11 to 1.21). As studies related to HDL-C were individually excluded, the trend of combined effect quantity remained as before exclusion, indicating good stability of the analysed results. After excluding study[19] which had the most heterogeneity, heterogeneity dropped to nil (p=0.728, I^2=0.0%) and the RR for CRC was 0.92 (95% CI 0.85 to 0.99).

DISCUSSION

Only prospective studies were included in this meta-analysis, which minimised bias that is usually a concern in retrospective case–control studies. High levels of TG were found to be associated with an increased risk of CRC. High levels of TC were also associated with an increased risk of CRC. These observations help to resolve previous controversies. It is worth noting that the current analysis found that high serum HDL-C concentrations can reduce the risk of CRC, with little evidence of heterogeneity. These results establish the relationship between the lipid profile and the risk of CRC and help predict the occurrence of CRC.

After the exclusion of three studies with high heterogeneity, sensitivity analysis showed no heterogeneity, and that high concentrations of TC increased the risk of CRC. Furthermore, a case–control study showed that higher levels of TC significantly reduced CRC risk. The same study reported that the cancer group, which partially consisted mainly of patients in the advanced stage, had lower TC than the control group.[9] It is hypothesised that the inverse relationship between serum TC and CRC risks results from metabolic or nutritional changes in patients with advanced CRC, rather than increased levels as a protective factor for CRC. In the late stages of CRC, TC concentration decreases due to metabolic changes, competition and rapid consumption of nutrients by cancer cells.[2]

Previous studies have not found a relationship between serum HDL-C levels and CRC risks.[14 20 28] Until 2011, only a nested case–control study showed that high levels of HDL-C reduced the risk of CRC and RR by 0.54 (95% CI 0.39 to 0.77).[19] The current comprehensive analysis of all prospective studies associated with HDL-C and CRC risk identified for the first time their relationship. In addition to obtaining results without heterogeneity, the results' stability was also proved by the sensitivity analysis.

When analysed by anatomical site, the results indicated a positive and significant association between TC and the risk of rectal cancer. On the contrary, there were no significant results for colon cancer, suggesting different causal factors between both anatomical sites.[39] When subgroup analysis stratified by study quality was carried out, TG, TC and HDL-C in high-quality studies were found to be significantly associated with CRC risk. However, in the relationship between TC and CRC risks, the groups with the number of cases of <338 had a more significant association and were not heterogeneous. This may be related to the fact that studies with a small sample size are more likely to show positive results. All studies related to TC ranged from small to large sample size, while the forest map did not show apparent heterogeneity among studies with increased sample size.

Stratified analysis of the subgroups by follow-up years revealed a significant positive association for TG with CRC risks was only observed in the group of ≥13 years. When analysing the risks of TC and CRC, the group with a follow-up time of less than 13 years produced a positive result with less heterogeneity. A further evaluation must be included in the analysis to explain this situation.

When the subgroup analysis was performed by geographical location, a significant positive correlation was observed between TG and CRC risks in Europe. The difference in TG concentration between different research groups was large, while the difference in European studies was relatively small. These differences may be due to regional differences. However, more studies are needed to obtain more reliable evidence, as previous studies are limited in number.

An analysis of gender found that high levels of TG in men are associated with a higher risk of CRC than in women, although the results are highly heterogeneous. High TC levels in female patients are more likely to cause CRC. This may be related to changes in endogenous hormones, but this needs further investigation. In addition, with adjustment of confounding factors, the estimated values of TG and TC for CRC risk decreased while the estimates of HDL-C increased. Adjusting confounding factors also did not reveal a statistically significant correlation between LDL-C at diagnosis and CRC risk.

Some studies have shown that in the process of tumour immunity, immune cells, such as activated T cells, experience rapid proliferation and need to absorb a large amount of cholesterol. Cholesterol is sourced from LDL-C, demonstrating the benefits of LDL-C. Therefore, increasing LDL can help immune cells fight tumour cells.[40] Furthermore, cholesterol helps to establish a mature immune synapse to target and kill cancer cells.[41] Elevated LDL-C levels were observed in patients with cancer cachexia, which may be due to intermediate density lipoprotein (IDL) accumulation, cholesterol

deficiency and LDL-C particle formation. LDL-C has a low affinity for their receptors and persists in the circulation, and this phenomenon is gradually aggravated with the decrease in skeletal muscle. Therefore, the increase in LDL-C can be understood as a secondary phenomenon in patients with cachexia.[42]

Strengths and limitations

The main strengths of the present systematic review and meta-analysis are its comprehensive, prospective design, large sample size and long follow-up time. Many case data ensure the effectiveness of statistical results and a comprehensive evaluation of the relationship between blood lipids and CRC risks. Furthermore, the final result of the current study is supported by high-quality studies and a thorough sensitivity analysis. None of the included studies was rated as having a severe risk of bias, without evidence of publication bias. These factors could further enhance the credibility of the analysis's outcome.

Nevertheless, although a large number of subgroups and sensitivity analyses have not identified these variations as statistically significant sources of heterogeneity, significant heterogeneity still exists in the study results, which may limit the effectiveness of the overall pooled results. This may be because some factors that may affect the incidence are not included, such as life behaviour and eating habits, comorbidities and psychological factors.

Another limitation is that heterogeneity may be introduced, although clear inclusion criteria were used because of differences in comparison methods. Comparing the highest reading of the serum lipid group with the lowest group would produce different estimates, creating heterogeneity. For example, the definitions for high and low categories of blood lipids were different in the initial studies. The studies used different cut-off values, such as classifying blood lipid indexes into two or five categories. A much higher number of studies with high and low lipid levels would help produce higher risk estimates.

Third, demographic differences (male vs female) may have caused significant heterogeneity, which may be caused by differences in incidence rates and changes in endogenous hormone levels. Fourth, there was pronounced heterogeneity due to pathological differences in cancer. Different anatomical parts of the intestinal tract have unique microbial and immune environments. These microbiotas produce inflammatory and carcinogenic metabolites by metabolising lipids. This study cannot consider the impact of microorganisms on localised changes in the intestinal environment. Finally, selected studies were adjusted for major potential confounders. Thus, it cannot be ruled out that the observed correlations were due to unmeasured or residual confounders of other factors. For example, the consumption of statins cannot be adjusted due to the lack of corresponding records.

Implications

Our study suggests that dyslipidaemia may be a risk factor to consider when making clinical decisions on CRC screening and monitoring. These results are significant due to highly inconsistent data reported by numerous studies, which makes it difficult to conclude. The mechanism of hypertriglyceridaemia and the change in cholesterol outflow capacity may benefit future biological research on colon cancer carcinogenesis. More studies are needed to explore the mechanism of lipid metabolism represented by blood lipids in the occurrence of CRC. Evidence of a causal effect would facilitate blood lipid indicators for CRC screening. The ease of measuring lipid levels would further help control lipid metabolism in patients with CRC. In the future, a high-quality, large-scale, multicentre prospective study is needed to confirm the role of blood lipids in the risk of CRC.

CONCLUSION

In summary, this systematic review and meta-analysis demonstrated that high serum levels of TG and TC were positively correlated with the incidence rate of CRC. On the contrary, high serum HDL-C levels were negatively correlated with the incidence rate of CRC. In particular, no association was found between LDL-C and CRC risks. Further clinical studies are needed to verify whether intervention in the concentration of lipid components would reduce CRC incidence.

Contributors BR conceived the study. All authors were involved in the study design during weekly meetings. ZY and HT designed and performed the search strategy. SL and XS screened the titles and abstracts for eligibility. ZY and HT extracted the data (quantitative data) and SL and XS reviewed the study quality (qualitative data). ZY and HT analyzed the data. ZY wrote the first draft. All authors revised this draft for critical content. All authors approved the final manuscript. BR, ZY and HT are the guarantors. All persons listed as authors have contributed to preparing the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Online supplemental data are available at BMJ Open Online.

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