

Review Article

The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis

Yun Tian^{1,†}, Keming Wang^{1,†}, Juan Li^{1,†}, Jirong Wang¹, Zhaoxia Wang¹, Yingrui Fan¹, Ying Ye², Guozhong Ji³ and Yi Li^{4,*}

¹Department of Oncology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China; ²Emergency Center, Affiliated Hospital of Xuzhou Medical College, Xuzhou, People's Republic of China; ³Institute of Digestive Endoscopy and Medical Center for Digestive Diseases, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China; ⁴Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, No. 305 East Zhongshan Road, Nanjing 210002, People's Republic of China

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Abstract

Objective: There have been inconsistent results published regarding the relationship between dyslipidaemia and an increased risk of colorectal neoplasia (CRN), including colorectal adenoma (CRA) and colorectal cancer (CRC). We conducted a meta-analysis to explore the relationship between dyslipidaemia and CRN.

Design: We identified studies by performing a literature search using PubMed, EMBASE and the Science Citation Index through October 2013.

Setting: We analysed thirty-three independent studies reporting the association between CRN and at least one of the selected lipid components, including total cholesterol (TC), TAG, HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C).

Subjects: CRN cases (n 21 809) were identified.

Results: Overall, people with high levels of serum TAG (risk ratio (RR) = 1.08; 95 % CI 1.05, 1.12, $P < 0.00001$) and LDL-C (RR = 1.07; 95 % CI 1.00, 1.14, $P = 0.04$) presented an increased prevalence of CRN. Subgroup analyses revealed that high levels of serum TC (RR = 1.04; 95 % CI 1.01, 1.09, $P = 0.02$), TAG (RR = 1.06; 95 % CI 1.03, 1.10, $P = 0.0009$) and LDL-C (RR = 1.11; 95 % CI 1.04, 1.19, $P = 0.003$) increased the risk of CRA but not of CRC. No association between serum HDL-C and risk for CRN (including CRA and CRC) was observed.

Conclusions: Both TAG and LDL-C were significantly associated with an increasing prevalence of CRN. High levels of serum TC, TAG and LDL-C were positively associated with CRA but not with CRC. No significant association was observed between levels of serum HDL-C and CRN.

Keywords
Serum lipids
Colorectal adenoma
Colorectal cancer
TAG
Meta-analysis

Colorectal cancer (CRC) is reported to be the fourth most commonly diagnosed cancer and is the second most common cause of cancer deaths in North America⁽¹⁾. CRC is believed to arise from colorectal adenoma (CRA) through a sequence from adenoma to adenocarcinoma as a consequence of a limited set of molecular events that largely originate with a relatively benign adenoma that progresses to cancer⁽²⁾. Accumulated data indicate that metachronous lesions occur at a rate of 20 to 30 % per year in post-polypectomy patients. The propensity to develop

CRA identifies a sizeable subgroup of the population at an enhanced risk for subsequent adenoma formation and colorectal carcinoma. This indicates that identifying risk factors associated with CRN is essential for the reduction of colorectal carcinoma.

The positive association between obesity and CRA prevalence demonstrates an underlying dose–response relationship according to BMI⁽³⁾. Timely screening of obese patients for CRA is thus recommended. Dyslipidaemia is an important component of metabolic syndrome and is demonstrated to contribute to colorectal tumorigenesis through insulin resistance, oxidative stress and inflammatory

† The first three authors contributed equally to this work.

pathways⁽⁴⁾. Alteration of serum lipids (high TAG and low HDL-cholesterol (HDL-C)) has been linked to an increased risk of CRA^(5,6) and several types of malignancy including CRC⁽⁷⁾. A recent large case-control study indicated that a high level of serum TAG was significantly associated with a larger number of adenomas⁽⁸⁾. Although several studies have explored the dyslipidaemia component, e.g. lipid and lipoprotein concentrations individually in relation to CRN risk, there is still inconsistency for this issue. More importantly, the association between components of serum lipids and CRN risk is largely unknown.

An increased understanding between the development of CRN and dyslipidaemia can clarify the mechanistic steps linking components of serum lipids and CRN and may be useful in determining the benefits of early CRN screening. Unfortunately, data on the relationship of serum lipid levels with CRA/CRC are contradictory. Some studies have established a positive association between serum total cholesterol (TC) level and CRN. If this theory were correct, it may contribute to an excess in mortality in individuals with dyslipidaemia compared with those without the disorder. However, other studies showed no significant association between CRN and serum lipids^(9,10). Because the association between dyslipidaemia and CRN formation has not yet been systematically assessed, we conducted a systematic review and meta-analysis of all available studies evaluating this issue to investigate the association between components of serum lipids and CRN risk.

Materials and methods

The current review and meta-analysis follows the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement⁽¹¹⁾.

Search strategy

For the present analysis, a systematic literature search through October 2013 was performed in PubMed, EMBASE and the Science Citation Index to identify relevant studies. Studies investigating the relationship between serum lipids and CRN (including CRA and CRC) were carried out by searching for articles written in English. The search term comprised the following keywords: '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' 'colorectal adenoma, CRA' or 'colorectal neoplasm, CRN' (see online supplementary material, Supplemental Table 1 for the search strategy in PubMed). All references of the selected articles were checked, including manual searches. Additionally, to find any additional published studies, we interrogated references of all the articles. The titles and abstracts were scanned to exclude any clearly irrelevant studies. The full texts of the remaining articles were read to determine

whether they contained information on the topic of interest. All searches were conducted independently by two authors (Y.T. and Y.L.). The results were then compared; any questions or discrepancies were resolved by iteration and consensus.

Study selection

Only publications that fulfilled all of the following criteria were selected for the meta-analysis: (i) the study subjects were adults (older than 18 years); (ii) publication with a case-control, cross sectional, nested case-control or cohort study design; (iii) CRN incidence as the outcome of interest; (iv) reported an estimate of the association of CRN (defined as colorectal cancer or adenoma or both) in individuals with at least one of the selected lipid components (TC, TAG, HDL-C and LDL-cholesterol (LDL-C)); and (v) reported risk ratio (RR; or OR estimates in case-control studies) or hazard ratios (HR) with estimates of their corresponding 95% CI (or sufficient data to evaluate the above effects).

Data extraction

Information extracted from the extensive review of each publication included: (i) publication data (first author's name, year of publication and country of the population studied); (ii) type of study design; (iii) study participants' age range; (iv) sample size (cases and controls or cohort size); (v) type of lesion; (vi) risk estimates with their corresponding CI; (viii) method used to confirm the presence or absence of CRN; and (ix) colonoscopy examination at the time of diagnosis. OR from case-control studies were considered as an estimate of RR⁽¹²⁾. If a study provided several risk estimates, the most completely adjusted estimate was extracted and used in the meta-analysis. The information from each study was extracted by two independent researchers (Y.T. and Y.L.), with disagreements resolved with a majority vote by all authors.

Statistical analysis

All analyses, including publication bias, were performed using the computer program Review Manager version 5.1 (Oxford, UK). Study-specific risk estimates were extracted from each study and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. The heterogeneity of all publications was evaluated with the Cochran Q test and I^2 statistic⁽¹³⁾. An I^2 value of <30%, 30–50% and >50% was considered as little or no heterogeneity, moderate heterogeneity and severe heterogeneity, respectively. For the Q statistic, a P value of <0.1 was considered to have significant heterogeneity. Summaries of RR estimates were evaluated using both fixed-effects and random-effects methods. Random effects are used when heterogeneity is present. Initial analysis, including all studies, was performed to look for an association between serum lipids and CRN. Subgroup analyses were also carried out to estimate the components of serum

lipids and the risk of CRC and CRA. For meta-analysis results, the P value of <0.05 indicated statistical significance. A funnel plot for potential publication bias analysis was conducted using the statistical software package Stata 11.0 with Begg⁽¹⁴⁾ and Egger tests⁽¹⁵⁾.

Results

Study characteristics

Two hundred and eighty-five publications relevant to the words searched were retrieved using the methodology and the search terms described above. Of these, eighty-two duplicated publications were excluded. The remaining 203 studies were selected for further evaluation based on information from abstracts and titles. After screening abstracts and titles, forty-seven studies were considered to be relevant to our study subject. Fourteen articles were excluded as they did not investigate the association of serum lipids with risk of CRN. In total, thirty-three records that met the detailed inclusion criteria were included in the present meta-analysis^(4,6,8-10,16-43). All studies reported on at least one of the serum lipid components (TC, TAG, HDL-C and LDL-C) and the risk of CRN. Details of these studies are described in Tables 1 and 2.

Overall analyses on the association of serum lipids and colorectal neoplasm

The association between serum TC and risk of CRN was analysed first. The sixteen studies on TC (four cohort, five cross-sectional and seven case-control studies) were published between 1990 and 2013 (Tables 1 and 2) and involved a total of 21 809 CRN cases^(4,9,10,19-22,25,28,29,34,36,38,39,42,43). Three studies were conducted in the USA^(20,38,39), one in Sweden⁽⁴²⁾, three in Korea^(9,10,22), five in Japan^(25,28,29,36,43), one in Finland⁽²¹⁾, one in Germany⁽¹⁹⁾ and two in European countries^(4,24) (Tables 1 and 2). A random-effects model was considered for a summary RR as there was evidence of heterogeneity for the included sixteen studies ($Q=45.28$, P value for heterogeneity = 0.00001 , $I^2=65\%$). The overall RR for CRN (adenoma or colon cancer) associated with serum TC was 1.00 (95% CI 0.93, 1.08, $P=0.93$; Fig. 1(a)), while the funnel plot for potential publication bias was also analysed (Fig. 1(b)). Our result indicated that there was no statistical evidence of publication bias (Egger's $P=0.638$, Begg's $P=0.837$).

There were twenty-nine studies reported on TAG (twelve cohort studies, four cross-sectional and thirteen case-control studies) published between 1990 and 2013 and involved a total of 31 546 CRN cases (Tables 1 and 2)^(4,6,8-10,16-18,20,22-24,26-32). Nine studies were conducted in the USA^(16,18,20,32,35,37-40), one in Sweden⁽⁴²⁾, five in Korea^(6,9,10,22,27), two in China^(23,30), eight in Japan^(8,24,26,28,29,31,36,43), one in Austria⁽⁴¹⁾ and three in European countries^(4,17,34) (Tables 1 and 2). Pooled analysis

showed a significant association between serum TAG and CRN (n 29 studies; summary RR = 1.08; 95% CI 1.05, 1.12, $P<0.00001$; Fig. 2(a)). A random-effects model was considered for a summary RR because of the significant heterogeneity of the included twenty-nine studies ($Q=110.44$, P value for heterogeneity <0.00001 , $I^2=68\%$). The funnel plot for potential publication bias was also implemented (Fig. 2(b)); the results of the statistical analysis showed a potential publication bias (Egger's $P=0.006$, Begg's $P=0.225$).

Next, we performed an analysis to evaluate the association between serum LDL-C and risk of CRN. There were a total of eight studies carried out on LDL-C (three cohort studies, three cross-sectional and two case-control studies) published between 1993 and 2013 which included 12 473 CRN cases (Tables 1 and 2)^(4,9,10,19,26,29,33,42). One study was conducted in the USA⁽³³⁾, one in Sweden⁽⁴²⁾, one in Germany⁽¹⁹⁾, two in Korea^(9,10), two in Japan^(26,29) and one in European countries⁽⁴⁾ (Tables 1 and 2). Data provided evidence that LDL-C is an increased risk factor of CRN development (summary RR = 1.07; 95% CI 1.00, 1.14, $P=0.04$; Fig. 3(a)). A random-effects model was considered for summary RR due to the existence of heterogeneity of the included eight studies ($Q=79.32$, P value for heterogeneity <0.00001 , $I^2=90\%$), while the funnel plot for potential publication bias was also conducted (Fig. 3(b)). Results of the statistical analysis showed no significant publication bias (Egger's $P=0.573$, Begg's $P=0.835$).

Finally, we performed analysis of studies to evaluate the association between HDL-C and CRN. The included twenty-three studies on HDL-C (ten cohort studies, four cross-sectional and nine case-control studies) were published between 1990 and 2013 (Tables 1 and 2) and involved a total of 21 426 CRN cases^(4,6,9,10,16-21,23,24,26-31,33,37-39,42). Seven studies were conducted in the USA^(16,18,20,33,37-39), one in Sweden⁽⁴²⁾, one in Germany⁽¹⁹⁾, two in China^(23,30), four in Korea^(6,9,10,27), five in Japan^(24,26,28,29,31), one in Finland⁽²¹⁾ and two in European countries^(4,17) (Tables 1 and 2). A random-effects model was considered for a summary RR as there was significant heterogeneity of the included twenty-three studies ($Q=63.10$, P value for heterogeneity = 0.0001 , $I^2=57\%$). Analysis of the twenty-three studies indicated that HDL-C was not significantly associated with CRN (RR = 1.03; 95% CI 0.98, 1.07, $P=0.25$; Fig. 4(a)), while the funnel plot for potential publication bias was also analysed (Fig. 4(b)). Our result indicated that there was no statistical evidence of publication bias (Egger's $P=0.983$, Begg's $P=0.252$).

Overall analyses on the association of serum lipids and colorectal cancer

Eight publications in the present meta-analysis on TC (four cohort and four case-control studies) and risk of CRC were published between 1992 and 2012 and involved a total of 10 979 CRC cases (Table 1)^(4,21,22,25,34,38,42,43). One study

Table 1 Studies contributing to the analysis of serum lipids and colorectal cancer

Author/reference and country	Study population	Age (years)	Type of lesion	Serum lipid measurement, RR (95% CI), start to end	Controlled variables
Cohort studies					
Ahmed <i>et al.</i> (2006) ⁽¹⁶⁾ , USA	15 792 general American population	45–64	194 colorectal cancers, including 139 colon cancers	TAG, 1.08 (0.8, 1.5) HDL-C, 1.19 (0.9, 1.6)	Gender, race, education, sports index, age
Inoue <i>et al.</i> (2009) ⁽²⁴⁾ , Japan	27 724 general Japanese population	40–69	155; 102 colon cancers, 53 rectal cancers	HDL-C, 1.13 (0.8, 1.6) TAG, 0.84 (0.6, 1.2)	Age, smoking habits, physical activity, weekly ethanol intake
Iso <i>et al.</i> (2009) ⁽²⁵⁾ , Japan	33 368 general Japanese population	40–69	320 colorectal cancers (217 men and 103 women)	TC, 1.03 (0.9, 1.2)	Age, smoking, ethanol intake, BMI, blood pressure, diabetes, vegetable consumption, coffee
Schoen <i>et al.</i> (1999) ⁽³³⁾ , USA	5849 general American population	74	102 colorectal cancers	HDL-C, 0.6 (0.3, 1.2) LDL-C, 0.5 (0.3, 0.8)	Gender, race, age, income, marital status, smoking, alcoholic consumption, aspirin use, physical activity, fat and vegetable consumption
Tsushima <i>et al.</i> (2005) ⁽⁴⁰⁾ , USA	7619 Japanese-American	Not reported	500: 376 colon and 124 rectal cancers	TAG, 1.07 (0.8, 1.4)	BMI, heart rate, cigarette smoking, alcohol use, total energy
Wulaningsih <i>et al.</i> (2012) ⁽⁴²⁾ , Sweden	540 309 general Swedish population	44	3982: 2472 colon cancers, 1510 rectal cancers	TC, 1.12 (1.0, 1.3) LDL-C, 0.81 (0.5, 1.3) TAG, 1.18 (1.1, 1.3) HDL-C, 1.3 (1.0, 1.7)	Age, gender, socio-economic status
Bowers <i>et al.</i> (2006) ⁽²¹⁾ , Finland	28 983 Finnish male smokers	57	227 colon cancer cases 183 rectal cancer cases	HDL-C, 1.09 (0.80, 1.49) TC, 0.74 (0.54, 1.01)	Age, smoking, TC
Stocks <i>et al.</i> (2010) ⁽³⁴⁾ , Norway, Austria, Sweden	578 700 general population	65 (men) 64 (women)	2834 men and 1861 women with colorectal cancer	TC, 1.00 (0.94, 1.06) TC, 1.08 (1.00, 1.17) TAG, 1.17 (1.06, 1.29) TAG, 1.02 (0.91, 1.14)	Age, smoking, and individual components of metabolic abnormalities
Stürmer <i>et al.</i> (2006) ⁽³⁵⁾ , USA	22 071 healthy male physicians	40–84	494 colorectal cancers	TAG, 0.9 (0.7, 1.2)	Age, exercise, smoking, alcohol use, non-steroidal anti-inflammatory drugs
Trevisan <i>et al.</i> (2001) ⁽³⁷⁾ , USA, Italy	21 311 men and 15 991 women	20–69	41 men and 13 women with colorectal cancer	HDL-C, 0.92 (0.48, 1.76) TAG, 1.01 (0.83, 1.23)	Age, drinking alcoholic beverages, smoking
Ulmer <i>et al.</i> (2009) ⁽⁴¹⁾ , Austria	71 693 men and 84 460 women	Not reported	600 colon cancers 273 rectal cancers	TAG, 1.08 (0.81, 1.44) TAG, 1.56 (1.00, 2.43)	Age and gender

Table 1 Continued

Author/reference and country	No. of cases/controls	Source of controls	Age (years)	Type of lesion	Serum lipid measurement, RR (95% CI), start to end	Controlled variables
Case-control studies Chung <i>et al.</i> (2006) ⁽²²⁾ , Korea	105/105	Hospital	59	105 colorectal cancers	TAG, 0.6 (0.3, 1.2) TC, 0.3 (0.1, 0.9)	Age and gender
Trichopoulos <i>et al.</i> (1992) ⁽³⁶⁾ , USA	100/100	Hospital	Not reported	100 colorectal cancers	TC, 0.53 (0.4, 0.7) HDL-C, 0.45 (0.3, 0.7) TAG, 0.81 (0.5, 1.3)	Age and gender
van Duijnhoven <i>et al.</i> (2011) ⁽⁴⁾ , European countries	1238/1238	Hospital	59	1238 colorectal cancers	TC, 0.92 (0.8, 1.0) HDL-C, 0.83 (0.7, 1.0) LDL-C, 0.93 (0.8, 1.1) TAG, 1.03 (0.9, 1.2)	Age, gender, centre, follow-up time, time of blood collection and fasting status
Aleksandrova <i>et al.</i> (2011) ⁽¹⁷⁾ , Germany, Denmark, France, Greece, Italy, Spain, Netherlands, UK	1093/1093	Registry data	59	689 colon cancers 404 rectal cancers	TAG, 1.36 (0.95, 1.95) TAG, 1.00 (0.70, 1.43) HDL-C, 1.36 (1.04, 1.78) HDL-C, 0.91 (0.63, 1.31)	Study centre, gender, age at blood collection, follow-up time since blood collection, time of the day at blood collection and fasting status, (among women) menopausal status
Saydah <i>et al.</i> (2003) ⁽³²⁾ , USA	173/346	CLUE II cohort	Not reported	132 colon cancers 41 rectal cancers	TAG, 0.69 (0.41, 1.16)	Age
Yamada <i>et al.</i> (1998) ⁽⁴³⁾ , Japan	129/258	Hospital	55	129 colorectal cancers	TC, 2.0 (1.0, 4.1) TAG, 3.0 (1.4, 6.43)	Gender, age, date of examination, history of prior health check-up

RR, risk ratio; HDL-C, HDL-cholesterol; TC, total cholesterol; LDL-C, LDL-cholesterol.

Table 2 Studies contributing to the analysis of serum lipids and colorectal adenoma

Author/reference and country	No. of cases/controls	Source of controls	Age (years)	Type of lesion	Serum lipid measurement, RR (95% CI), start to end	Controlled variables
Case-control studies						
Bird <i>et al.</i> (1996) ⁽²⁰⁾ , USA	486/520	Hospital	62	486 left colon and rectum adenomas	TC, 1.2 (0.8, 1.8) TAG, 1.5 (1.0, 2.3) HDL-C, 1.6 (0.9, 2.8)	Gender and age
Chung <i>et al.</i> (2006) ⁽²²⁾ , Korea	105/105	Hospital	58	105 colorectal adenomas	TAG, 1.2 (0.5, 2.9) TC, 0.7 (0.3, 1.6)	Age and gender
Park <i>et al.</i> (2000) ⁽⁹⁾ , Korea	134/134	Hospital	Not reported	134 male colorectal adenomas	TAG, 2.98 (1.2, 7.4) TC, 2.44 (0.6, 10.0) HDL-C, 2.23 (0.8, 6.2) LDL-C, 1.31 (0.4, 4.3)	Age and gender
Hu <i>et al.</i> (2011) ⁽²³⁾ , Taiwan	397/2709	Hospital	52	379 colorectal adenomas	TAG, 1.18 (0.91, 1.53) HDL-C, 0.94 (0.71, 1.24)	Non-polyp/cancer control
Kim <i>et al.</i> (2007) ⁽⁶⁾ , Korea	731/1800	Hospital	54	731 colorectal adenomas	TAG, 1.16 (0.96, 1.40) HDL-C, 1.07 (0.84, 1.36)	Non-polyp/cancer control
Morita <i>et al.</i> (2005) ⁽³¹⁾ , Japan	756/1751	Hospital	49–57	756 male colorectal adenomas	TAG, 1.18 (0.98, 1.42) HDL-C, 0.85 (0.61, 1.18)	Not reported
Otani <i>et al.</i> (2006) ⁽⁸⁾ , Japan	782/738	Hospital	61	782 colorectal adenomas	TAG, 1.5 (1.1, 2.05)	Not reported
Tsilidis <i>et al.</i> (2010) ⁽³⁹⁾ , USA	132/260	CLUE II cohort	55	132 colorectal adenomas	TC, 0.97 (0.49, 1.92) HDL-C, 0.92 (0.45, 1.90) TAG, 0.85, 0.40, 1.81	Age, gender, race, date of blood draw, fasting
Author/reference and country						
	Enrolment	Study population	Age (years)	Colonoscopy	Type of lesion	Serum lipid measurement, RR (95% CI), start to end
Cross-sectional studies						
Bayendorffer <i>et al.</i> (1993) ⁽¹⁹⁾ , Germany	1988–1989	822 consecutive patients	52–45	Yes	194 colorectal adenomas	HDL-C, 0.61 (0.4, 0.9) LDL-C, 1.91 (1.6, 2.3) TC, 1.36 (0.8, 2.3)
Kono <i>et al.</i> (1990) ⁽²⁸⁾ , Japan	1986–1988	1297 men	49–56	Yes	88 male colorectal adenomas	TC, 1.3 (0.7, 2.4) HDL-C, 0.6 (0.3, 1.2) TAG, 1.5 (0.8, 2.8)
Kono <i>et al.</i> (1993) ⁽²⁹⁾ , Japan	1988–1990	1363 men	48–56	Yes	138 left-sided colon adenomas	TC, 0.8 (0.4, 1.6) HDL-C, 1.1 (0.6, 2.0) LDL-C, 0.8 (0.5, 1.3) TAG, 0.8 (0.5, 1.3)

Table 2 Continued

Tabuchi <i>et al.</i> (2006) ⁽³⁶⁾ , Japan	1995–2003	4887 patients	10–94	Yes	3821 colorectal tubular adenomas	TC, 1.04 (1.0, 1.1) TAG, 1.13 (1.0, 1.3)
Yang <i>et al.</i> (2013) ⁽¹⁰⁾ , Korea	2006–2009	19 281 consecutive participants	40–79	Yes	5958: 5504 non-advanced colorectal adenomas and 454 advanced colorectal adenomas	TC, 1.13 (0.9, 1.4) HDL-C, 1.09 (1.0, 1.2) LDL-C, 1.19 (1.1, 1.3) TAG, 1.36 (1.2, 1.5)
Author/reference and country	Study population	Age (years)	Type of lesion	Serum lipid measurement, RR (95% CI), start to end	Controlled variables	
Cohort studies						
Ashbeck <i>et al.</i> (2009) ⁽¹⁹⁾ , USA	392 individuals from Wheat Bran Fiber trial and the Ursodeoxycholic Acid trial	66	770 non-advanced neoplasia 333 advanced neoplasia	TAG, 0.97 (0.78, 1.21) TAG, 0.87 (0.64, 1.18) TAG, 1.28 (0.92, 1.78) TAG, 0.88 (0.56, 1.38) HDL-C, 0.94 (0.74, 1.19) HDL-C, 0.87 (0.63, 1.20) HDL-C, 1.28 (0.89, 1.84) HDL-C, 0.86 (0.52, 1.42)	Age and study	
Kim <i>et al.</i> (2012) ⁽²⁷⁾ , Korea	6438 Korean participants in the Colorectal Polyp Registry	Not reported	1771 patients with colorectal adenomatous polyps	HDL-C, 1.13 (0.8, 1.6) TAG, 0.84 (0.6, 1.2)	Age, education, occupation, household income, marital status	
Liu <i>et al.</i> (2010) ⁽³⁰⁾ , China	4872 general Chinese population	50	719 colorectal adenoma	TAG, 1.26 (1.04, 1.53) HDL-C, 1.30 (1.10, 1.54)	Age, gender, smoking, alcohol	
Kaneko <i>et al.</i> (2010) ⁽²⁶⁾ , Japan	727 Japanese population	Not reported	727 colon tumours	TAG, 1.00 (0.99, 1.01) TAG, 1.01 (1.00, 1.02) LDL-C, 1.00 (0.98, 1.02) LDL-C, 1.00 (0.99, 1.01) HDL-C, 1.01 (1.00, 1.02) HDL-C, 1.02 (1.00, 1.04)	Age, dietary intake	

RR, risk ratio; TC, total cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

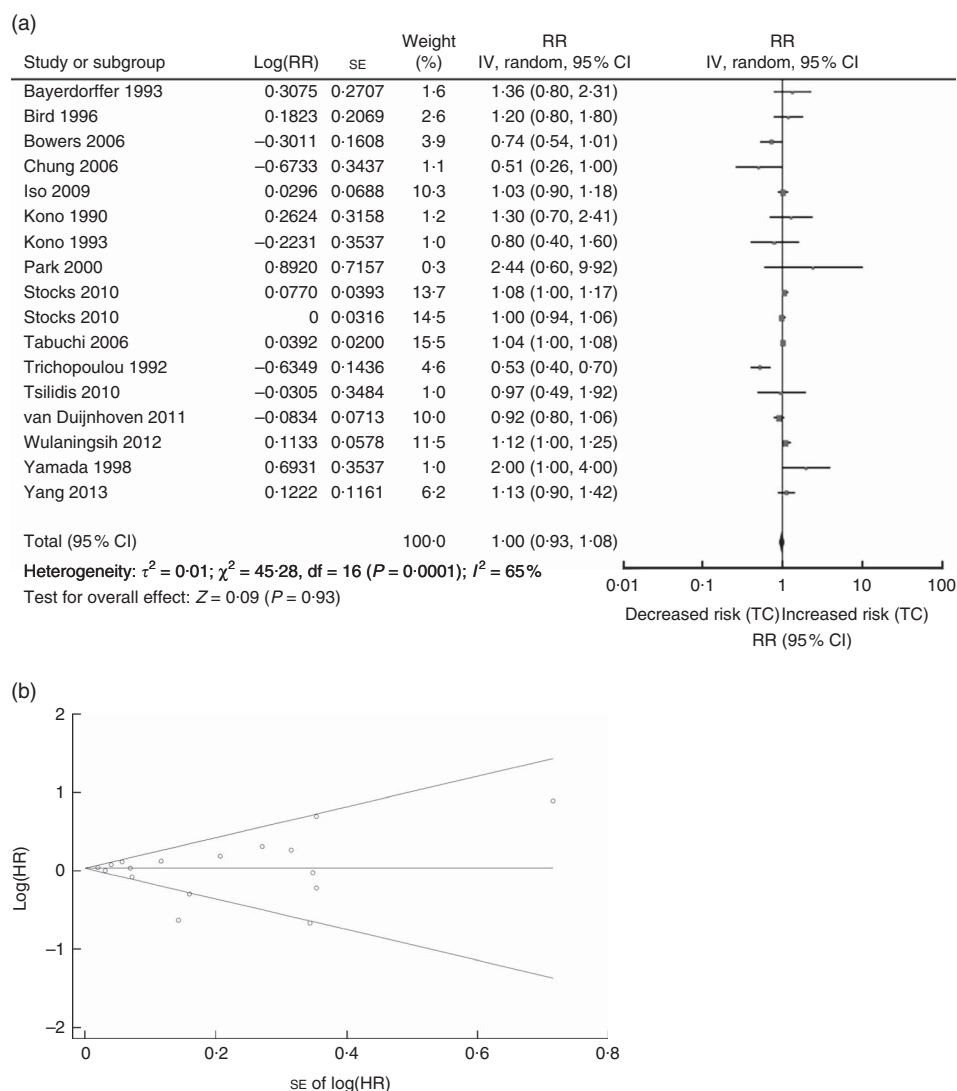


Fig. 1 Association between TC and CRN (adenoma and cancer combined): (a) forest plot; (b) funnel plot. In (a), the study-specific RR and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95 % CI. In (b), Begg's funnel plot with pseudo 95 % CI is presented (TC, total cholesterol; CRN, colorectal neoplasm; RR, risk ratio; IV, fixed-effects model; HR, hazard ratio)

was conducted in the USA⁽³⁸⁾, one in Sweden⁽⁴²⁾, one in Korea⁽²²⁾, two in Japan^(25,43), one in Finland⁽²¹⁾ and two in European countries^(4,34) (Table 1). Pooled data did not support the association between TC and CRC (RR=0.95; 95 % CI 0.85, 1.06, $P=0.38$). There was a statistically significant heterogeneity among studies ($Q=40.30$, P value for heterogeneity <0.00001 , $I^2=80\%$; Table 3).

The association between serum TAG and risk of CRC was analysed. Fourteen studies on TAG (eight cohort and six case-control studies) and risk of CRC were published between 1992 and 2012 and involved a total of 13 785 CRC cases (Table 1)^(4,16,17,22,24,32,34,35,37,38,40-43). Six studies were conducted in the USA^(16,32,35,37,38,40), one in Sweden⁽⁴²⁾, one in Korea⁽²²⁾, one in Austria⁽⁴¹⁾ two in Japan^(24,43) and three in European countries^(4,17,34) (Table 1). The association of serum TAG with CRC risk was not observed (RR = 1.07; 95 %

CI 0.99, 1.15; $P=0.10$). A random-effects model was constructed as there was statistically significant heterogeneity among studies ($Q=31.81$, P value for heterogeneity = 0.01, $I^2=50\%$; Table 3).

The association between serum HDL-C and risk of CRC was then analysed in our study. Nine studies on HDL-C (six cohort and three case-control studies) and risk of CRC were published between 1992 and 2012 and involved a total of 7328 CRC cases (Table 1)^(4,16,17,21,24,33,37,38,42). Four studies were conducted in the USA^(16,33,37,38), one in Sweden⁽⁴²⁾, one in Japan⁽²⁴⁾, one in Finland⁽²¹⁾ and two in European countries^(4,17) (Table 1). The pooled RR of serum HDL-C for CRC was 0.97 (95 % CI 0.80, 1.18, $P=0.77$), suggesting no significant relevance. Statistically significant heterogeneity existed among studies ($Q=33.01$, P value for heterogeneity = 0.0001, $I^2=73\%$; Table 3).

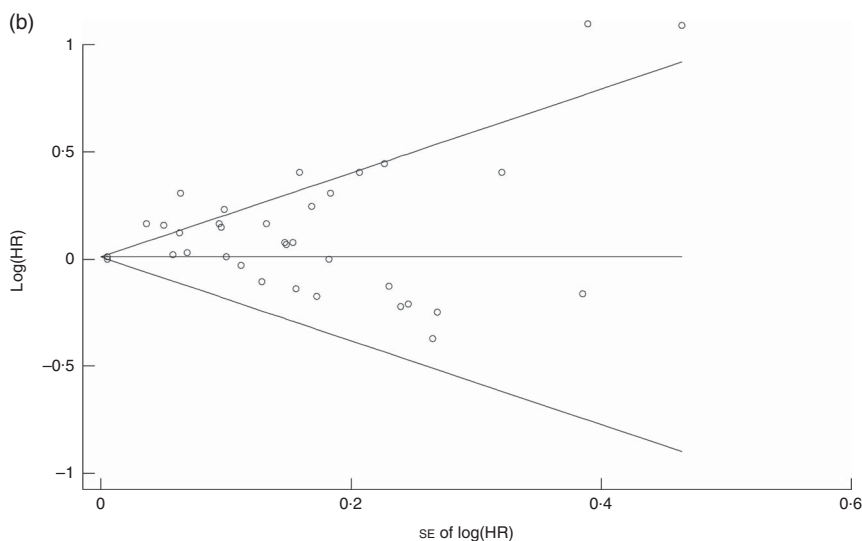
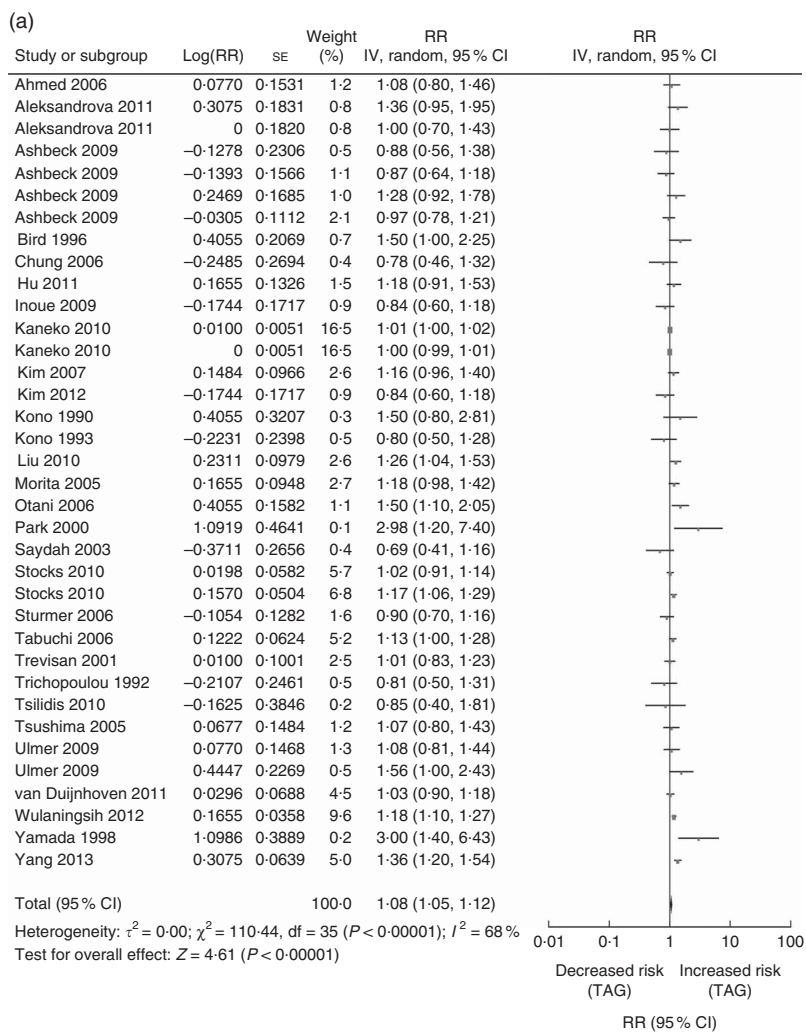


Fig. 2 Association between TAG and CRN (adenoma and cancer combined): (a) forest plot; (b) funnel plot. In (a), the study-specific RR and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95 % CI. In (b), Begg's funnel plot with pseudo 95 % CI is presented (CRN, colorectal neoplasm; RR, risk ratio; IV, fixed-effects model; HR, hazard ratio)

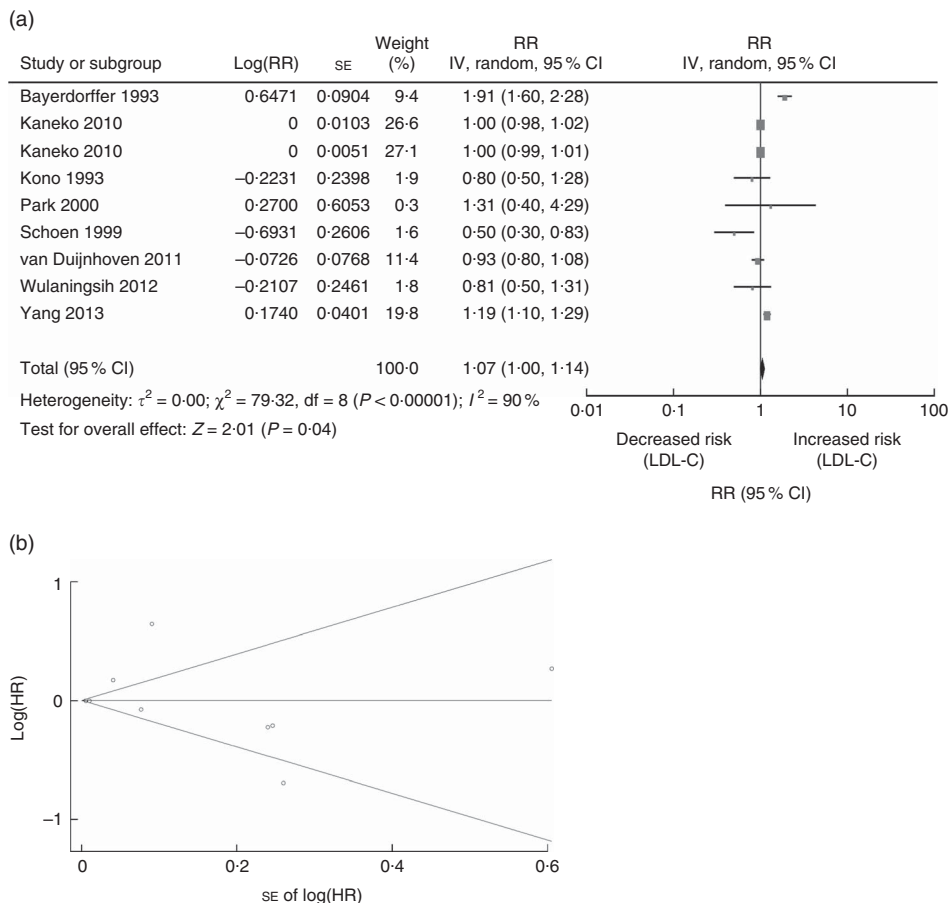


Fig. 3 Association between LDL-C and CRN (adenoma and cancer combined): (a) forest plot; (b) funnel plot. In (a), the study-specific RR and 95 % CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95 % CI. In (b), Begg's funnel plot with pseudo 95 % CI is presented (LDL-C, LDL-cholesterol; CRN, colorectal neoplasm; RR, risk ratio; IV, fixed-effects model; HR, hazard ratio)

There were three studies regarding LDL-C (two cohort and one case-control study) and risk of CRC that were published between 1990 and 2013 and involved a total of 5322 CRC cases (Table 1)^(4,33,42). One study was conducted in the USA⁽³³⁾, one in Sweden⁽⁴²⁾ and one in European countries⁽⁴⁾ (Table 1). The association between serum LDL-C and CRC risk was not observed (RR=0.88; 95 % CI 0.77, 1.01, $P=0.07$). A fixed-effects model was used as there was no statistically significant heterogeneity among studies ($Q=5.34$, P value for heterogeneity = 0.07, $I^2=63\%$; Table 3).

Overall analyses on the association of serum lipids and colorectal adenoma

Nine studies reporting associations between TC (five cross-sectional and four case-control studies) and risk of CRA were published between 1990 and 2013 and involved a total of 10 935 CRA cases (Table 2)^(9,10,19,20,22,28,29,36,39). Two studies were conducted in the USA^(20,39), one in Germany⁽¹⁹⁾, three in Korea^(9,10,22) and three in Japan^(28,29,36) (Table 2). The results from nine studies showed that serum

TC had a significant association with risk of CRA (RR=1.04; 95 % CI 1.01, 1.09, $P=0.02$) and there was no significant heterogeneity among these studies ($Q=5.26$, P value for heterogeneity = 0.73, $I^2=0\%$; Table 3).

We next performed a meta-analysis specifically for TAG and risk of CRA. The sixteen studies on TAG (four cohort studies, four cross-sectional and eight case-control studies) and risk of CRA were published between 1990 and 2013 and involved a total of 17 830 CRA cases (Table 2)^(6,8-10,18,20,22,23,26-31,36,39). Three studies were conducted in the USA^(18,20,39), five in Korea^(6,9,10,22,27), two in China^(23,30) and six in Japan^(8,26,28,29,31,36) (Table 2). The pooled RR for CRA was 1.06 (95 % CI 1.03, 1.10, $P=0.0009$) which indicated that serum TAG was significantly associated with CRA development. Significant between-study heterogeneity was found in this analysis ($Q=62.15$, P value for heterogeneity < 0.00001, $I^2=69\%$; Table 3).

There were fourteen studies on HDL-C (four cohort studies, four cross-sectional and six case-control studies) and risk of CRA published between 1990 and 2013 and involved a total of 14 098 CRA cases (Table 2)^(6,9,10,18-20,23,26-31,39).

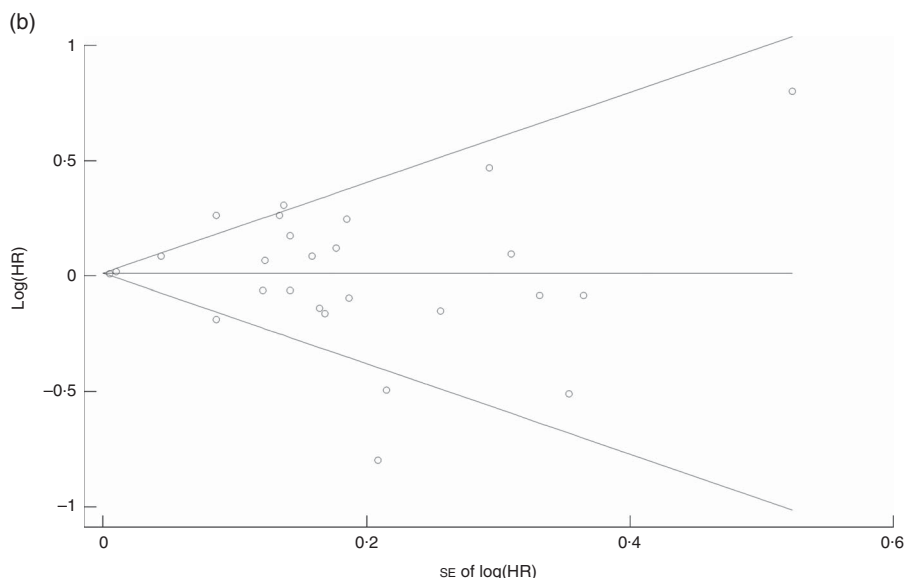
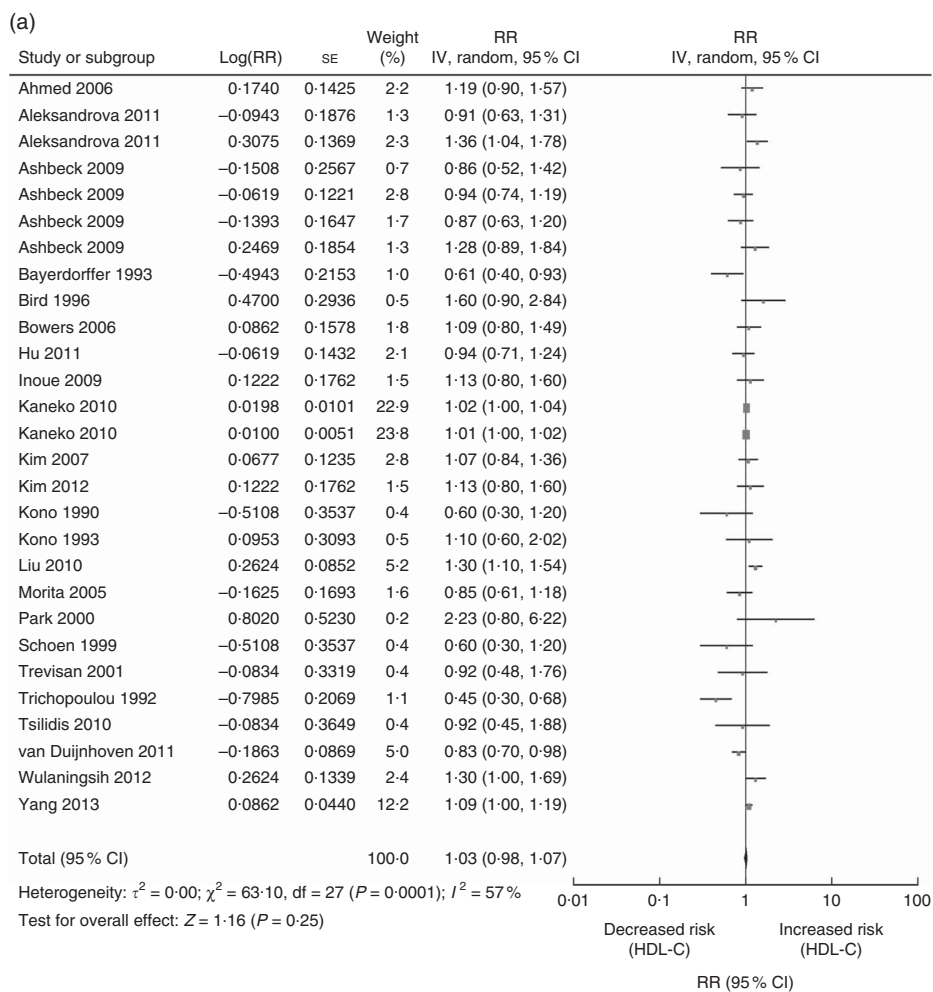


Fig. 4 Association between HDL-C and CRN (adenoma and cancer combined): (a) forest plot; (b) funnel plot. In (a), the study-specific RR and 95% CI are represented by the black square and horizontal line, respectively; the area of the black square is proportional to the specific-study weight to the overall meta-analysis. The centre of the diamond presents the pooled RR risk and its width represents the pooled 95% CI. In (b), Begg's funnel plot with pseudo 95% CI is presented (HDL-C, HDL- cholesterol; CRN, colorectal neoplasm; RR, risk ratio; IV, fixed-effects model; HR, hazard ratio)

Table 3 Summary risk estimates of the association between serum lipids and colorectal cancer and adenoma risk

Number of studies	<i>P</i>	RR	95 % CI	Heterogeneity test		
				<i>P</i>	<i>Q</i>	<i>I</i> ² (%)
TC and colorectal cancer risk						
Eight	0.38	0.95	0.85, 1.06	<0.00001	40.30	80
TAG and colorectal cancer risk						
Fourteen	0.10	1.07	0.99, 1.15	0.01	31.81	50
HDL-C and colorectal cancer risk						
Nine	0.77	0.97	0.80, 1.18	0.0001	33.01	73
LDL-C and colorectal cancer risk						
Three	0.07	0.88	0.77, 1.01	0.07	5.34	63
TC and colorectal adenoma risk						
Nine	0.02	1.04	1.01, 1.09	0.73	5.26	0
TAG and colorectal adenoma risk						
Sixteen	0.0009	1.06	1.03, 1.10	<0.00001	62.15	69
HDL-C and colorectal adenoma risk						
Fourteen	0.12	1.03	0.99, 1.06	0.03	29.88	43
LDL-C and colorectal adenoma risk						
Five	0.003	1.11	1.04, 1.19	<0.00001	70.43	93

RR, risk ratio; TC, total cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

Three studies were conducted in the USA^(18,20,39), one in Germany⁽¹⁹⁾, two in China^(23,30), four in Korea^(6,9,10,27) and four in Japan^(26,28,29,31) (Table 2). A pooled analysis of these fourteen studies showed that the RR for CRA with serum HDL-C was 1.03 (95 % CI 0.99, 1.06, *P* = 0.12) with a significant heterogeneity indicated (*Q* = 29.88, *P* value for heterogeneity = 0.03, *I*² = 43 %; Table 3).

Finally, we performed a meta-analysis specifically for the association between LDL-C and risk of CRA. Five studies on LDL-C (one cohort study, three cross-sectional and one case-control study) and risk of CRA were published between 1990 and 2013 and involved a total of 7151 CRA cases (Table 2)^(9,10,19,26,29). One study was conducted in Germany⁽¹⁹⁾, two in Korea^(9,10) and two in Japan^(26,29) (Table 2). Because there was statistical heterogeneity among studies (*Q* = 70.43, *P* value for heterogeneity < 0.00001, *I*² = 93 %), the random-effects model was applied. The pooled RR for CRA was 1.11 (95 % CI 1.04, 1.19, *P* = 0.003) which presented an increased risk for CRA (Table 3).

Subgroup and sensitivity analyses

The association of lipid components with risk for CRN was performed by subsets within the study design, geographic area, age, gender or the number of cases. Table 4 presents detailed results of subgroup analyses.

We performed a sensitivity analyses to explore the heterogeneity among studies of serum lipids and CRN. By using a stepwise process, we determined that most of the heterogeneity was accounted for in two studies^(21,38) reporting the association between TC and CRN. After excluding the two studies, there was no study heterogeneity (*P* = 0.15, *I*² = 27 %) and the RR for CRN was 1.04 (95 % CI 1.01, 1.07). Most of the heterogeneity was accounted for in eight studies^(8–10,32,34,36,42,43) reporting the association between TAG and CRN. After excluding these studies, there was no study heterogeneity (*P* = 0.11,

*I*² = 26 %) and the RR for CRN was 1.01 (95 % CI 1.00, 1.01). We found that most of the heterogeneity was accounted for in two studies^(10,19) reporting the association between HDL-C and CRN. After excluding the two studies, there was no study heterogeneity (*P* = 0.14, *I*² = 38 %) and the RR for CRN was 1.00 (95 % CI 0.99, 1.01). Most of the heterogeneity was accounted for in four studies^(17,19,30,38) reporting the association between LDL-C and CRN. After excluding these studies, there was no study heterogeneity (*P* = 0.16, *I*² = 23 %) and the RR for CRN was 1.01 (95 % CI 1.00, 1.02).

Discussion

Our data clearly indicated the positive association between serum TAG and LDL-C and the increased risk of CRN. Subgroup analysis indicated that serum TAG was associated with an increased risk of CRA, but not CRC. It remains uncertain whether TAG is the causal factor responsible for increasing the risk of CRA but not for CRC, although several mechanisms have tried to explain the association between increasing TAG levels and CRN risk. Serum TAG plays an important role in insulin-like growth factor-1 levels⁽⁴⁴⁾, a hormone with proliferative and anti-apoptotic effects. It is demonstrated that the insulin/insulin-like growth factor-1 pathway increases the activity of the ras protein occurring in abnormal colonocytes and stimulates the progression of adenomas into cancers through mediating mitogenicity by activation of K-ras⁽⁴⁵⁾. Additionally, hypertriglyceridaemia also increases pro-inflammatory cytokines, including IL-6 and TNF- α , while decreasing anti-inflammatory cytokines such as IL-10. The increased inflammatory response has been linked to DNA damage and to effects on the growth, apoptosis and proliferation of colorectal tumour cells. Furthermore, high

Table 4 Results of subgroup analysis of serum lipids and colorectal neoplasm risk

Subgroup	No. of studies	<i>P</i>	RR	95% CI	Heterogeneity test	
					<i>P</i>	<i>I</i> ² (%)
TC and colorectal neoplasm risk						
Study design						
Cohort	4	0.32	1.04	0.97, 1.11	0.07	53
Case-control	7	0.65	0.93	0.66, 1.29	0.0003	76
Cross-sectional	5	0.03	1.04	1.00, 1.08	0.64	0
Study location						
Asia	9	0.02	1.04	1.01, 1.08	0.17	31
Europe	4	0.75	1.01	0.93, 1.10	0.03	64
USA	3	0.54	0.83	0.46, 1.50	0.003	82
Age (years)						
<60	9	0.92	0.99	0.83, 1.18	0.02	57
≥60	2	0.19	1.03	0.98, 1.08	0.24	30
Gender composition						
Male	3	0.56	1.14	0.73, 1.77	0.32	13
Female and male	13	0.99	1.00	0.93, 1.08	0.0001	70
No. of cases						
<1000	11	0.72	0.96	0.75, 1.22	0.0002	71
≥1000	5	0.01	1.04	1.01, 1.07	0.18	34
TAG and colorectal neoplasm risk						
Study design						
Cohort	12	0.01	1.04	1.01, 1.07	0.0001	64
Case-control	13	0.02	1.16	1.02, 1.32	0.01	52
Cross-sectional	14	0.05	1.19	1.00, 1.43	0.05	62
Study location						
Asia	15	0.001	1.07	1.03, 1.11	0.0001	77
Europe	4	0.0001	1.13	1.08, 1.18	0.14	40
USA	9	0.95	1.00	0.91, 1.09	0.43	2
Age (years)						
<60	11	0.0001	1.16	1.10, 1.22	0.10	36
≥60	4	0.08	1.11	0.99, 1.24	0.04	52
Gender composition						
Male	4	0.24	1.25	0.86, 1.81	0.07	58
Female and male	25	0.0001	1.08	1.04, 1.11	0.0001	69
No. of cases						
<1000	20	0.07	1.03	1.00, 1.07	0.0001	58
≥1000	11	0.003	1.10	1.03, 1.18	0.02	48
HDL-C and colorectal neoplasm risk						
Study design						
Cohort	10	0.004	1.01	1.00, 1.02	0.08	37
Case-control	9	0.68	0.96	0.79, 1.17	0.0001	69
Cross-sectional	4	0.39	0.85	0.59, 1.23	0.02	69
Study location						
Asia	12	0.10	1.03	0.99, 1.07	0.02	51
Europe	4	0.53	1.07	0.86, 1.34	0.008	71
USA	7	0.46	0.92	0.74, 1.14	0.005	62
Age (years)						
<60	11	0.79	1.02	0.88, 1.18	0.002	63
≥60	3	0.82	0.98	0.84, 1.14	0.17	35
No. of cases						
<1000	17	0.46	1.02	0.97, 1.07	0.0001	60
≥1000	6	0.47	1.04	0.93, 1.17	0.03	52
LDL-C and colorectal neoplasm risk						
Study design						
Cohort	3	0.85	1.00	0.97, 1.02	0.05	62
Case-control	2	0.38	0.94	0.81, 1.09	0.57	0
Cross-sectional	5	0.003	1.11	1.04, 1.19	0.0001	93
Study location						
Asia	3	0.23	1.28	0.86, 1.90	0.0001	93
Europe	2	0.25	0.92	0.80, 1.06	0.59	0
USA	1	0.008	0.50	0.30, 0.83	–	–
Age (years)						
<60	4	0.80	1.06	0.66, 1.72	0.0001	93
≥60	1	0.008	0.50	0.30, 0.83	–	–
Gender composition						
Male	2	0.48	0.86	0.55, 1.32	0.45	0
Female and male	6	0.03	1.08	1.01, 1.15	0.0001	92
No. of cases						
<1000	5	0.10	1.07	0.99, 1.15	0.0001	92
≥1000	3	0.87	1.02	0.82, 1.27	0.007	80

RR, risk ratio; TC, total cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

levels of serum TAG may also result in oxidative stress and in the development of reactive oxygen species⁽⁴⁶⁾, which could damage DNA and affect carcinogenesis by affecting gene expression, mutation and chromosomal rearrangement⁽⁴⁷⁾. Serum TAG may also affect colorectal tumorigenesis by mechanisms involving modification of bile acid excretion, circulating hormones and energy supply to neoplastic cells⁽⁴⁸⁾. Experiments with animal models indicated that *Apc*-deficient mice showed age-dependent hypertriglycerolaemia and a number of intestinal polyp formations, which could be suppressed by anti-hyperlipidaemic medicines. This was confirmed by another report that azoxymethane injection in obese rats with hypertriglycerolaemia resulted in an increased number of advanced colon aberrant crypt foci, which are putative precursors of colon cancer⁽⁴⁹⁾. In *Apc*-deficient FAP model mice, because of the reduced activity of the lipoprotein lipase, serum TAG and intestinal polyp formation decreased significantly after systemic administration of a PPAR ligand⁽⁵⁰⁾. Although the biological or molecular mechanism is unclear so far, experiments with animal models most likely showed a clear association between TAG and intestinal neoplasms. Further laboratory and epidemiological studies are still necessary to shed light on the association between serum TAG and CRN development.

Our meta-analysis showed no positive association between TC level and the prevalence of CRN or CRC, although a suggestive association was observed in CRA. A prospective study showed a significant association between serum TC and CRC, which also indicated the risk was higher in patients with colon cancer than with rectal cancer⁽⁵¹⁾. The possible association between TC and colorectal tumorigenesis may be at least partly caused by genetic factors, such as an apoE phenotype which affects both cholesterol metabolism and susceptibility to carcinoma⁽⁵²⁾. However, the pooled results of our study did not provide evidence for the association between TC and CRN. In our study, we found different associations of serum TC with CRA and CRC. Further research including a large number of studies is necessary to clarify this issue.

In our meta-analysis, higher levels of serum LDL-C were significantly associated with an increasing prevalence of CRN, while serum HDL-C levels were not significantly associated with a decreasing prevalence of CRN. Subgroup analysis demonstrated the positive association between serum LDL-C and CRA, although it was not associated with CRC. HDL-C, however, did not associate with either CRA or CRC. Previous studies have demonstrated that lipids and lipoproteins have been associated with neoplastic processes such as inflammation⁽⁵³⁾, insulin resistance and oxidative stress. Although there are several possible mechanisms whereby serum lipoproteins influence CRC, little is known regarding the mechanisms by which LDL-C and HDL-C participate in colorectal carcinogenesis. Further mechanistic studies are needed to understand the

deferent roles of LDL-C and HDL-C in the development of CRA as well as advanced carcinoma.

The other important finding is that none of the components of serum lipids included in the present meta-analysis (TAG, TC, HDL-C and LDL-C) was significantly correlated with the development of CRC, although positive associations between serum TAG, TC and LDL-C and CRA were found. It was previously reported the significant association of LDL-C with low-grade but not with high-grade CRA⁽²⁶⁾, a stronger correlation between high levels of serum TAG and the number of adenomas, and different associations of serum lipids and adenomas according to histological examination⁽⁸⁾. With the accumulated data, it is difficult to interpret the different effects of serum lipids on CRA and CRC because of the limited mechanisms that have demonstrated a clear biological plausibility for differential effects of lipids on the development of adenoma and advanced carcinoma. Because the potential effects of lipid parameters on different stages of colorectal carcinogenesis have not yet been established, this provides a potential chance for further study.

Our meta-analysis of studies with large numbers of incident cases provides high statistical power for estimating the relationship between components of serum lipids and prevalence of CRN. Despite the strength of the meta-analysis, our study also has several limitations. First, several studies we included are observational. Second, a meta-analysis is not able to solve problems with confounding factors because it did not take into account other possible confounding variables such as dietary patterns, family history of colon cancer and alcohol use, which might be associated with the risk of CRN. However, most studies in the meta-analysis adjusted for other known and potential risk factors for CRN development. Third, heterogeneity may be introduced because of methodological and demographic differences among studies, although appropriate well-motivated inclusion criteria were used. Fourth, the RR values of the baseline serum lipids were endorsed by different panels/organizations in the original studies. Finally, the individual studies may adjust for different covariates including diets, which may affect our results. It is reported that several attributes of diet (such as alcohol and high intake of saturated fats) appear to alter levels of individual lipids^(54,55). Many of these diets, which determine serum lipid levels, are established risk factors for CRN^(56,57). Therefore, dietary factors might be an important confounding factor in our study.

Conclusion

In conclusion, the present systematic review and meta-analysis demonstrated that high levels of serum TAG and LDL-C are positively associated with the prevalence of CRN. In addition, persons with high levels of the serum lipid components TC, TAG and LDL-C have a greater risk

of suffering from CRA but not CRC. Neither CRA nor CRC is linked with serum HDL-C levels. Given the rise in the epidemic of dyslipidaemia worldwide, health-care providers should be more vigilant and adhere with colorectal carcinogenesis screening guidelines in subjects with dyslipidaemia, especially those with abnormal serum TAG, TC and LDL-C levels.

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Supplementary material

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/S1368980015000646>

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