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META-ANALYSIS

Association of cholesterol with risk of pancreatic cancer: A meta-analysis

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Abstract

AIM: To evaluate the effect of dietary cholesterol and serum total cholesterol (TC) on the risk of pancreatic cancer.

METHODS: A literature search was performed up to June 2014 in PubMed, EMBASE, China National Knowledge Infrastructure and China Biology Medical literature database for relevant articles published in English or Chinese. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated with a random-effects model.

RESULTS: We included 14 published articles with 439355 participants for dietary cholesterol, and 6 published articles with 1805697 participants for serum TC. For the highest *vs* lowest category of dietary cholesterol, the pooled RR (95%CI) of pancreatic cancer was 1.308 (1.097-1.559). After excluding two studies (RR > 3.0), the pooled RR (95%CI) was 1.204 (1.050-1.380). In subgroup analysis stratified by study design, the pooled RRs (95%CIs) were 1.523 (1.226-1.893) for case-control studies and 1.023 (0.871-1.200) for cohort studies. The association of dietary cholesterol with the risk of pancreatic cancer was significant for studies conducted in North America [1.275 (1.058-1.537)] and others [2.495 (1.565-3.977)], but not in Europe [1.149 (0.863-1.531)]. No significant association [1.003 (0.859-1.171)] was found between the risk of pancreatic cancer and serum TC.

CONCLUSION: Dietary cholesterol may be associated with an increased risk of pancreatic cancer in worldwide populations, except for Europeans. The results need to be confirmed further.

Key words: Dietary cholesterol; Serum total cholesterol; Pancreatic cancer; Risk; Meta-analysis

Core tip: Many epidemiological studies have explored the association of cholesterol with the risk of pancreatic cancer, but the results of these studies are conflicting. We conducted the current meta-analysis to evaluate the effect of dietary cholesterol and serum total cholesterol on the risk of pancreatic cancer. The results suggested that dietary cholesterol may be associated

with an increased risk of pancreatic cancer. However, the finding needs to be confirmed further.

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INTRODUCTION

Pancreatic cancer is an uncommon but fatal malignant tumor. The overall 5-year survival rate of pancreatic cancer is less than 4%[1]. Worldwide, the estimated numbers of cases and deaths for pancreatic cancer are 277000 and 266000 in 2008[2], respectively. In the United States, the estimated numbers of new pancreatic cancer cases and deaths are 46420 and 39590 in 2014[3], respectively. Several factors have been associated with the risk of pancreatic cancer, such as age[4], body mass index (BMI)[5], smoking[6], coffee drinking[7], hepatitis B virus (HBV) and hepatitis C virus (HCV) infection[8], type 2 diabetes mellitus[9] and family history[10]. In addition, many nutritional factors, such as folate[11], fat[12] and cholesterol[13-16], might also have an influence on the risk of pancreatic cancer.

Several epidemiologic studies have been performed to evaluate the relationship between cholesterol and the risk of pancreatic cancer. Although some studies found that dietary cholesterol was associated with an increased risk of pancreatic cancer[13-15], others demonstrated no association between dietary cholesterol and the risk of pancreatic cancer[17-19]. The association between serum total cholesterol (TC) and the risk of pancreatic cancer also remains controversial[16,20,21]. So far, there is no sufficient epidemiological evidence to establish an association between the risk of pancreatic cancer and dietary cholesterol or serum TC level.

Therefore, we conducted a meta-analysis to evaluate the effect of dietary cholesterol and serum TC on the risk of pancreatic cancer.

MATERIALS AND METHODS

Search strategy

A literature search was performed up to June 2014 for relevant available articles published in English or Chinese from the following databases: (1) PubMed; (2) EMBASE; (3) China National Knowledge Infrastructure (CNKI); and (4) China Biology Medical literature database (CBM). The following search terms were used: "pancreatic cancer OR pancreatic neoplasm OR pancreatic carcinoma OR pancreatic tumour" and "cholesterol OR hypercholesterolemia". Moreover, we reviewed the bibliographies of included articles to search additional studies not captured by our databases. The detailed steps of the literature search are shown in Figure 1.

Inclusion criteria

The inclusion criteria were as follows: (1) an observational study published as an original study to evaluate the association between the risk of pancreatic cancer and dietary cholesterol and serum TC; (2) the exposure of interest was cholesterol; (3) the outcome of interest was pancreatic cancer; and (4) relative risk (RR) and 95% confidence interval (CI) (or data to calculate these) were provided. The most recent and complete study was included if data from the same population had been published repeatedly.

Two investigators (JW and LZ) searched and reviewed all identified studies independently. If the two investigators cannot reach an agreement, it was resolved by consensus with a third reviewer.

Data extraction

The following data were extracted from each study by two investigators (JW and LZ) independently: the first author's name, publication year, country where the study was performed, study design, sample size and number of cases, mean age, male percentage in case (exposed) and control (unexposed) groups, RRs (we presented all results as RR for simplicity) with corresponding 95%CIs for highest *vs* lowest categories of cholesterol, the cut-points for cholesterol exposure and variables adjusted for in the analysis. We extracted the RRs that were adjusted for the most confounders.

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95%CI to assess the strength of association between cholesterol and the risk of pancreatic cancer. The I^2 was adopted to assess the heterogeneity between studies (I^2 values of 0%, 25%, 50% and 75% represent no, low, moderate and high heterogeneity[22], respectively). The random-effects model (REM) was used as the pooling method. Meta-regression was performed to evaluate the potentially important covariates that might exert substantial impacts on between-study heterogeneity[23]. Influence analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study[24]. The Egger *et al*[25] regression asymmetry test and the funnel plot were adopted to evaluate publication bias. Subgroup analysis was performed by study design (case-control or cohort study) and continent (North America, Europe or others).

All statistical analyses were performed with STATA version 10.0 (Stata Corporation, College Station, TX, United States). All reported probabilities (*P*-values)

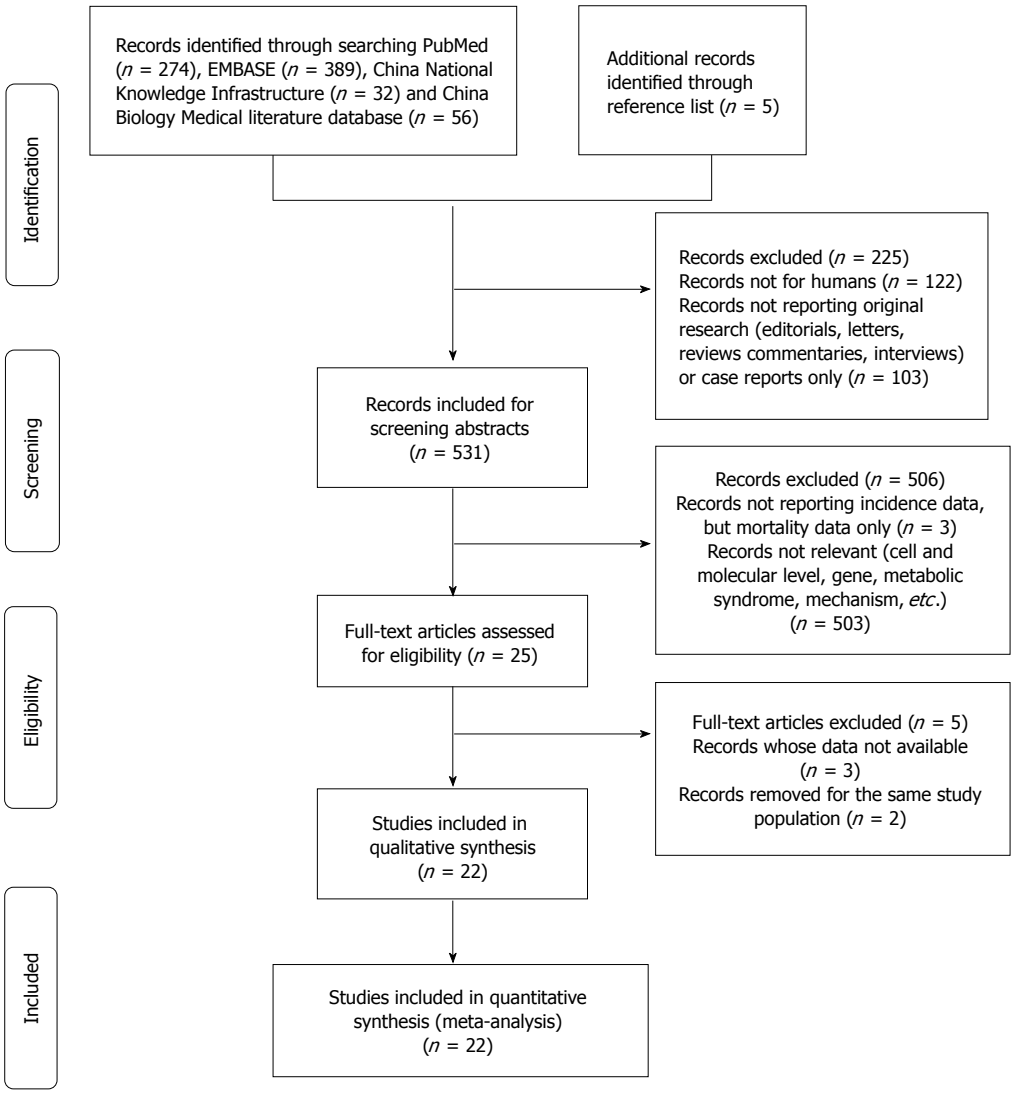

Figure 1 Flow diagram of literature search.

were two-sided with a statistical significance level of 0.05.

RESULTS

Study characteristics

For dietary cholesterol, 14 articles[13-15,17-19,26-33] with 14 studies (4 cohort studies and 10 case-control studies) were included, involving 439355 participants. For serum TC, 6 articles[16,20,21,34-36] with 8 studies (6 cohort studies and 2 case-control studies) were included, involving 1805697 participants. The detailed characteristics of the included studies are shown in Tables 1 and 2.

Quantitative synthesis

The main results are summarized in Table 3.

Dietary cholesterol and the risk of pancreatic cancer: For the highest *vs* lowest category of dietary cholesterol, the pooled RR of pancreatic cancer was 1.308 (95%CI: 1.097-1.559, I^2 = 55.3%, $P_{heterogeneity}$ = 0.006). The pooled RRs for case-control and cohort studies were 1.523 (95%CI: 1.226-1.893, I^2 = 49.7%, $P_{heterogeneity}$ = 0.037) and 1.023 (95%CI: 0.871-1.200, I^2 = 0.0%, $P_{heterogeneity}$ = 0.508), respectively. The pooled RRs for studies conducted in North America, Europe and others were 1.275 (95%CI: 1.058-1.537, I^2 = 29.3%, $P_{heterogeneity}$ = 0.215), 1.149 (95%CI: 0.863-1.531, I^2 = 55.4%, $P_{heterogeneity}$ = 0.047) and 2.495 (95%CI: 1.565-3.977, I^2 = 0.0%, $P_{heterogeneity}$ = 0.362), respectively (Figure 2).

Serum TC and the risk of pancreatic cancer: Serum TC level (highest *vs* lowest) was not significantly associated with the risk of pancreatic cancer (RR = 1.003, 95%CI: 0.859-1.171, I^2 = 55.5%, $P_{heterogeneity}$ = 0.028). The pooled RRs for European and Asian populations were 1.034 (95%CI: 0.722-1.481, I^2 = 65.1%, $P_{heterogeneity}$ = 0.035) and 1.005 (95%CI: 0.847-1.192, I^2 = 56.2%, $P_{heterogeneity}$ = 0.077), respectively.

Table 1 Characteristics of studies for dietary cholesterol included in the meta-analysis

Ref.	Country (year)	Study design	Mean age (case/control) Percentage of males (case/control)	Sample size (cases)	Cut-points for cholesterol exposure RR (95%CI)	Adjustment for covariates
Lin *et al*[13]	Japan	Case-control	64.7/65.1	327	Dietary cholesterol exposure (mg), < 206 (referent), 206-330, > 330 [2.06 (1.11-3.85)]	Age and pack-years of smoking
	-2005		NA	-109		
Chan *et al*[14]	United States	Case-control	NA	2233	Dietary cholesterol exposure (g/d) median, 122.8 (referent), 192.6, 257.6, 368.9 [1.5 (1.1-2.0)]	Age, sex, BMI, race, education, smoking, history of diabetes and energy intake
	-2007		54.7/51.9	-532		
Hu J *et al*[15]	Canada	Case-control	61.6/57.1	5667	Dietary cholesterol cut-point (mg/wk) < 966.261 (referent), 966.262-1412.753, 1412.754-1880.265, > 1880.266 [1.57 (1.09-2.26)]	Age, sex, BMI, province, education, alcohol drinking, pack year smoking, total of vegetable and fruit intake, saturated fat and total energy intake
	-2012		56.2/50.5	-628		
Howe *et al*[17]	Metropolitan Toronto	Case-control	64.6/64.8	754	Mean difference per day quartile 4-quartile 1 (569 mg) [0.95 (0.51-1.75)]	Caloric and fibre intake, lifetime cigarette consumption
	-1990		56.6/53.5	-249		
Bueno de Mesquita *et al*[18]	Netherlands	Case-control	NA	644	Dietary cholesterol [1.33 (0.72-2.45)]	Age, sex, response status, total smoking and dietary intake of energy
	-1991		54.9/48.3	-164		
Lucenteforte *et al*[19]	Italy	Case-control	NA	978	First quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first, fifth *vs* first [1.10 (0.68-1.77)]	Year of interview, education, tobacco smoking, history of diabetes and total energy intake
	-2010		53.4/53.4	-326		
Baghurst *et al*[26]	Australia	Case-control	NA	357	First quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first [3.19 (1.58-6.47)]	Age and pack-years of smoking
	-1991		50.0/56.1	-104		
Ghadirian *et al*[27]	Canada	Case-control	63.9/62.1	418	First quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first [2.24 (0.83-6.05)]	Age, sex, lifetime cigarette consumption, response status and total energy intake
	-1995		54.2/51.5	-179		
Heinen *et al*[28]	The Netherlands	Case-cohort	NA	120852	Dietary cholesterol (mg/d), first quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first, fifth *vs* first [0.78 (0.52-1.18)]	Age, sex, BMI, energy, smoking, alcohol, history of diabetes mellitus, history of hypertension, vegetables and fruits intake
	-2009		52.9/49.1	-350		
Kalapothaki *et al*[29]	Greece	Case-control	NA	362	Dietary cholesterol (mg), an increment of about one standard deviation of the energy-adjusted residual of the corresponding nutritional variable [1.19 (0.96-1.47)]	Age, sex, hospital, past residence, years of schooling, smoking, diabetes mellitus and energy intake
	-1993		NA	-181		
Michaud *et al*[30]	United States	Cohort	NA	88802	Median of cholesterol exposure (g/d) 212 (referent), 275, 322, 371, 466 [1.11 (0.67-1.83)]	Pack-years of smoking, BMI, history of diabetes mellitus, caloric intake, height, physical activity, menopausal status and glycemic load intake
	-2003		NA	-178		
Nöthlings *et al*[31]	Hawaii and Los Angeles	Cohort	65/60	190545	Cholesterol density (mg/1000 kcal per day) median intake 56.8 (referent), 81.6, 100.4, 120.8, 156.8 [1.09 (0.89-1.32)]	Age, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status and energy intake
	-2005		51.2/45.3	-482		
Stolzenberg-Solomon *et al*[32]	Finland	Cohort	58/57	27111	First quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first, fifth *vs* first [0.92 (0.53-1.59)]	Energy intake, age, years of smoking and energy-adjusted saturated fat intake
	-2002		NA	-163		
Zatonski *et al*[33]	Poland	Case-control	62.2/63.2	305	First quintile of cholesterol exposure (referent), second *vs* first, third *vs* first, fourth *vs* first [4.31 (1.60-11.59)]	Cigarette lifetime consumption and calories
	-1991		61.8/45.6	-110		

NA: Not available; BMI: Body mass index.

Table 2 Characteristics of studies for serum total cholesterol included in the meta-analysis

Ref.	Country (year)	Study design	Mean age (case/control) Percentage of males (case/control)	Sample size (cases)	Cut-points for cholesterol Exposure RR (95%CI)	Adjustment for covariates
Wu *et al*[16]	China (2012)	Case-control	59.3/59.3 58.6/58.6	840 (210)	Serum TC < 5.70 mmol/L (referent), ⩾ 5.70 mmol/L [1.793 (1.067-3.013)]	Age, sex, hypertension, HBV markers, the levels of HDL, LDL, Tri and Apo B
Stolzenberg-Solomon *et al*[20]	Finland (2002)	Cohort	NA	29048 (172)	Serum TC < 5.18 mmol/L (referent), ⩾ 5.18 mmol/L [0.88 (0.60-1.28)]	Age, years smoked, cigarettes smoked per day, self-reported history of diabetes and bronchial asthma, occupational activity and measured high blood pressure
Johansen *et al*[21]	Austria, Norway, and Sweden (2010)	Cohort	NA	289866 (543)	Serum TC mean level (mmol/L) 4.5 (referent), 5.3, 5.8, 6.4, 7.6 [0.70 (0.53-0.93)]	Age, BMI and smoking status
Johansen *et al*[21]	Austria, Norway, and Sweden (2010)	Cohort	NA	288834 (314)	Serum TC mean level (mmol/L) 4.4 (referent), 5.1, 5.7, 6.3, 1.11 [0.75 (0.53-1.64)]	Age, BMI and smoking status
Kitahara *et al*[34]	South Korea (2011)	Cohort	NA	756604 (1799)	Serum TC (mg/dL) < 160 (referent), 160-179, 180-199, 200-239, ⩾ 240 [0.88 (0.74-1.05)]	Smoking, drinking, fasting serum glucose, BMI, hypertension and physical activity
Kitahara *et al*[34]	South Korea (2011)	Cohort	NA	433115 (776)	Serum TC (mg/dL) < 160 (referent), 160-179, 180-199, 200-239, ⩾ 240 [0.96 (0.74-1.24)]	Smoking, drinking, fasting serum glucose, BMI, hypertension and physical activity
Kuzmickiene *et al*[35]	Lithuania (2013)	Cohort	NA	6788 (73)	Serum TC (mmol/L) < 5.20 (referent), 5.20-5.89, 5.90-6.62, ⩾ 6.63 [1.76 (0.87-3.55)]	Age, BMI, smoking status, alcohol consumption and education
Xu *et al*[36]	China (2011)	Case-control	61.4/60.74 59.3/60.5	602 (290)	Serum TC (mmol/L) < 5.72 (referent), ⩾ 5.72 [1.01 (0.88-1.17)]	Diabetes mellitus, smoking, hypertension, family history of cancer, history of gastrointestinal surgery, history of biliary disease, history of chronic pancreatitis and triglyceride

NA: Not available; BMI: Body mass index.

Sources of heterogeneity and sensitivity analysis

In order to explore the between-study heterogeneity, we performed univariate meta-regression with the covariates of sex, age, publication year, sample size, continent where the study was conducted and study design. For the analysis between the risk of pancreatic cancer and dietary cholesterol, study design was found to contribute significantly to the between-study heterogeneity (P = 0.037). After excluding two studies[26,33] (RR > 3.0), the heterogeneity was reduced to 29.4% ($P_{heterogeneity}$ =0.158), and the pooled RR was 1.204 (95%CI: 1.050-1.380). For the analysis between the risk of pancreatic cancer and serum TC, no covariate contributed significantly to the between-study heterogeneity.

Influence analysis

For the relationship between dietary cholesterol and the risk of pancreatic cancer, the summary RR (95%CI) ranged from 1.203 (95%CI: 1.079-1.341) to 1.291 (95%CI: 1.146-1.455) in influence analysis (Figure 3). For the relationship between serum TC and the risk of pancreatic cancer, the range was from 0.941 (95%CI: 0.840-1.054) to 1.003 (95%CI: 0.913-1.101).

Publication bias

Egger test and funnel plot showed no evidence of significant publication bias for the analysis between the risk of pancreatic cancer and dietary cholesterol (P = 0.107) (Figure 4) or serum TC (P = 0.204).

Table 3 Pooled relative risks of associations between pancreatic cancer and dietary cholesterol and serum total cholesterol

Cholesterol source	Subgroup	No. of studies	Pooled RR (95%CI) REM	I^2	$P_{heterogeneity}$
Dietary cholesterol	All studies	14	1.308 (1.097-1.559)	55.3%	0.006
	After excluding two studies[24,31] (RR > 3.0)	12	1.204 (1.050-1.380)	29.4%	0.158
	Study design				
	Case-control	10	1.523 (1.226-1.893)	49.7%	0.037
	Cohort	4	1.023 (0.871-1.200)	0.0%	0.508
	Continent				
	North America	6	1.275 (1.058-1.537)	29.3%	0.215
	Europe	6	1.149 (0.863-1.531)	55.4%	0.047
	Others	2	2.495 (1.565-3.977)	0.0%	0.362
Serum TC	All studies	8	1.003 (0.859-1.171)	55.5%	0.028
	Continent				
	Europe	4	1.034 (0.722-1.481)	65.1%	0.035
	Asia	4	1.005 (0.847-1.192)	56.2%	0.077

TC: Total cholesterol; REM: Random effect model.

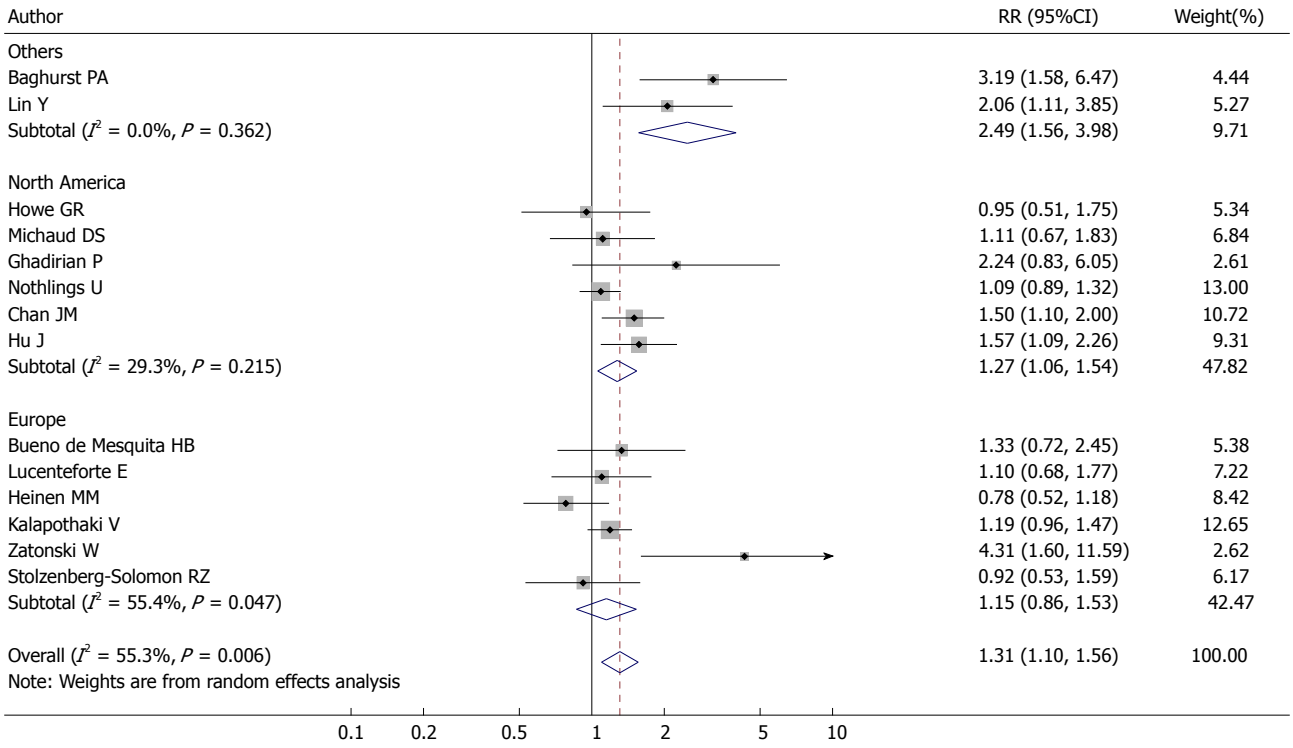

Figure 2 Forest plot of the relative risks of studies on dietary cholesterol and pancreatic cancer.

DISCUSSION

Recently, many studies have been performed to evaluate the association between cholesterol and the risk of pancreatic cancer. However, the results are conflicting. Generally, individual study has a relatively small sample size with insufficient power to detect the effect. Therefore, we conducted a meta-analysis to get a more reasonable conclusion. This meta-analysis, containing 439355 participants for dietary cholesterol and 1805697 participants for serum TC, can effectively assess the association of cholesterol and the risk of pancreatic cancer. Findings from this meta-analysis suggested that dietary cholesterol may be associated with an increased risk of pancreatic cancer. The association of dietary cholesterol with the risk of pancreatic cancer was significant in case-control studies, and for studies conducted in North America and others but not in Europe. No significant association between the risk of pancreatic cancer and serum TC was found in this meta-analysis.

The exact mechanism whereby high total cholesterol levels could lead to an increased risk of pancreatic cancer is unclear. There are several theories explaining the possible role of cholesterol in pancreatic cancer. Increased level of serum TC is related to increased levels of proinflammatory cytokines[37-39]. Longstanding pre-existing chronic pancreatitis is a strong risk factor for pancreatic cancer[40]. Moreover, dietary cholesterol may affect bile excretion. This may cause bile reflux

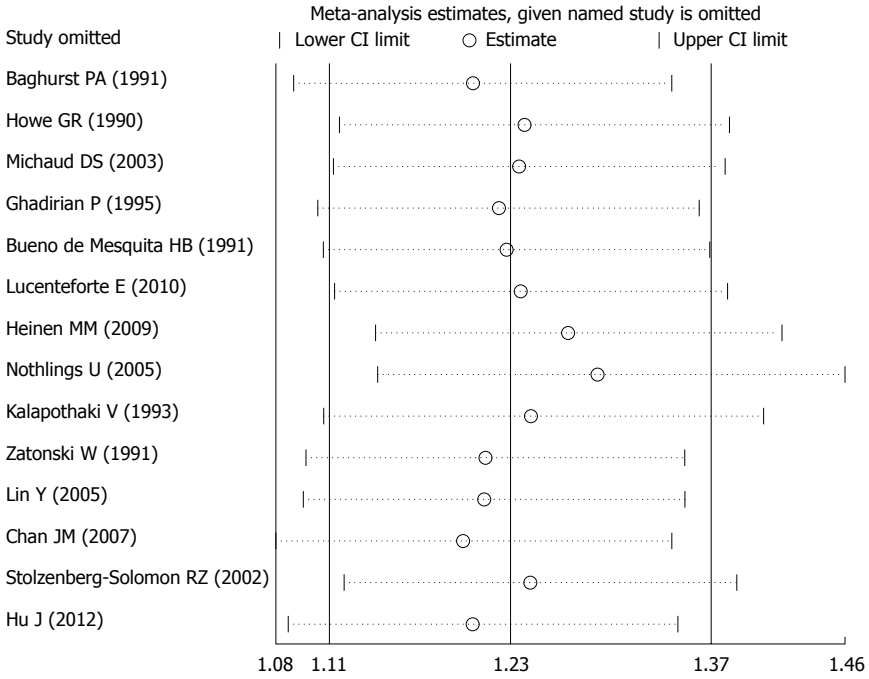

Figure 3 Influence analysis of individual study on the pooled estimate for studies on dietary cholesterol and pancreatic cancer.

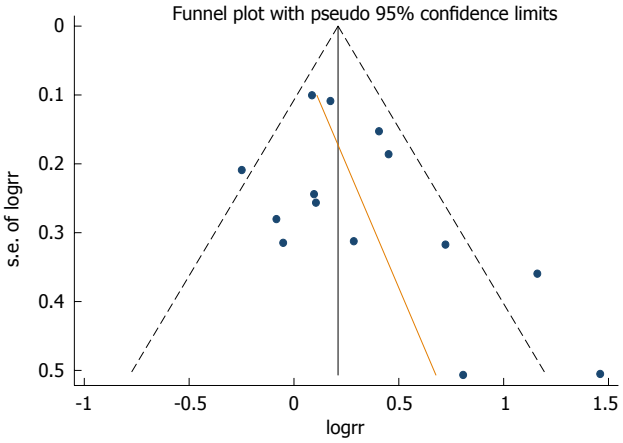

Figure 4 Funnel plot of the relative risks of 14 studies on dietary cholesterol and pancreatic cancer.

into the head of the pancreas *via* the common duct, where most tumors occur[26,41].

Between-study heterogeneity is common in meta-analysis. It is essential to explore the potential sources of between-study heterogeneity. Diversity in a number of indeterminate characteristics such as sex, age, publication year, sample size, the continent where the study was performed or study design might be the source of between-study heterogeneity. Therefore, we explored the potential sources of the between-study heterogeneity with meta-regression. However, only study design was found to contribute to the between-study heterogeneity significantly in the analysis for dietary cholesterol. In subgroup analysis by study design, the between-study heterogeneities for case-control studies and cohort studies were reduced to 49.7% and 0.0%, respectively. After excluding two studies[26,33] (RR > 3.0) in the analysis for dietary cholesterol, the between-study heterogeneity was reduced to 29.4%, and the result did not change substantially, suggesting that the result was stable.

This meta-analysis has several strengths. First, a large number of participants were included, allowing a much greater possibility of reaching a reasonable conclusion. Second, almost all studies included in this meta-analysis were adjusted for major risk factors, such as age, sex, smoking, BMI, energy intake, making the results more credible. Third, influence analysis showed that no individual study had an excessive influence on the pooled effects of dietary cholesterol and serum TC on the risk of pancreatic cancer. Fourth, after excluding two studies[26,33] (RR > 3.0) in dietary cholesterol analysis, the between-study heterogeneity was reduced to 29.4%, but the result did not change substantially.

However, the present study has several limitations. First, unknown confounders might result in exaggerating or underestimating the risk. Second, disparate results were found between the association of dietary cholesterol and serum TC with the risk of pancreatic cancer. Third, in subgroup analysis by continent, a significant association between dietary cholesterol and the risk of pancreatic cancer was found for studies conducted in North America and others, but no association was found for those in Europe. However, the discrepancy might also be caused by the relatively small number of studies in each subgroup analysis. Fourth, results from case-control studies are susceptible to recall bias, thus prospective cohort studies that do not suffer from recall bias are believed

to provide better evidence. However, only 4 cohort studies were included in this meta-analysis. Therefore, further cohort studies are warranted to confirm this association. In addition, patients might change their dietary habits after the diagnosis of pancreatic cancer; however, in most case-control studies included in this meta-analysis, the investigators collected the dietary information of participants at least 1 year before the interview. Finally, although serum TC was not found to be associated with the risk of pancreatic cancer, the blood of patients was collected after the diagnosis of pancreatic cancer in case-control studies and at the start of the study in cohort studies.

In summary, this meta-analysis suggested that dietary cholesterol may be associated with the risk of pancreatic cancer in worldwide populations, except for Europeans. The finding needs to be confirmed further.

COMMENTS

Background

Pancreatic cancer is an uncommon but fatal malignant tumor. Several factors have been associated with the risk of pancreatic cancer, but the association between cholesterol and the risk of pancreatic cancer is still unclear.

Research frontiers

Until now, many epidemiological studies have explored the association of cholesterol with the risk of pancreatic cancer, but the results of these studies are conflicting.

Innovations and breakthroughs

This is the first meta-analysis to investigate the association of cholesterol with the risk of pancreatic cancer. Dietary cholesterol may be associated with an increased risk of pancreatic cancer in worldwide populations, except for Europeans.

Applications

The results of our study may give people instructions to prevent pancreatic cancer by limiting cholesterol intake.

Peer-review

This manuscript presents a well-designed meta-analysis that assessed the association between cholesterol and the risk of pancreatic cancer. The results suggest that dietary cholesterol may be associated with an increased risk of pancreatic cancer in worldwide populations, except for Europeans.

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