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**Columns:** **META-ANALYSIS**

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

Wang J *et al*. Cholesterol and pancreatic cancer

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**Abstract**

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

**METHODS:** A literature search was performed up to Jun 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%CIs were calculated with random effects models.

**RESULTS:** We included 14 published articles with 439355 participants for dietary cholesterol, and 6 published articles with 1805697 participants for serum total cholesterol (TC). For the highest versus 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%CI) 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, except for European. The results need to be confirmed further.

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**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](#_ENREF_1)]. Worldwide, the estimated numbers of cases and deaths for pancreatic cancer are 277000 and 266000 in 2008[[2](#_ENREF_2)], respectively. In the United States, the estimated numbers of new pancreatic cancer cases and deaths are 46420 and 39590 in 2014[[3](#_ENREF_3)], respectively. Several factors have been associated with the risk of pancreatic cancer, such as age[[4](#_ENREF_4)], BMI[[5](#_ENREF_5)], smoking[[6](#_ENREF_6)], coffee drinking[[7](#_ENREF_7)], HBV and HCV infection[[8](#_ENREF_8)], type 2 diabetes mellitus[[9](#_ENREF_9)] and family history[[10](#_ENREF_10)]. In addition, many nutrition factors, such as folate[[11](#_ENREF_11)], fat[[12](#_ENREF_12)] and cholesterol[[13-16](#_ENREF_13)] 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](#_ENREF_13)], others demonstrated no association between dietary cholesterol and the risk of pancreatic cancer[[17-19](#_ENREF_17)]. The association between serum total cholesterol (TC) and the risk of pancreatic cancer also remains inconsistent[[16](#_ENREF_16),[20](#_ENREF_20),[21](#_ENREF_21)]. So far, there is no sufficient epidemiological evidence to establish an association between the risk of pancreatic cancer and dietary cholesterol and 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 Jun 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%CI (or data to calculate these) were provided. The most recent and complete study was included if one 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%CI for highest versus 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 I2 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](#_ENREF_22)], respectively). The random effect 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](#_ENREF_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](#_ENREF_24)]. Egger *et al*[[25](#_ENREF_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) were two-sides with a statistical significance level of 0.05.

**RESULTS**

***Studies characteristics***

For dietary cholesterol, 14 articles[[13-15](#_ENREF_13),[17-19](#_ENREF_17),[26-33](#_ENREF_26)] with 14 studies (4 cohort studies and 10 case-control studies) were included, involving 439355 participants. For serum TC, 6 articles[[16](#_ENREF_16),[20](#_ENREF_20),[21](#_ENREF_21),[34-36](#_ENREF_34)] with 8 studies (6 cohort studies and 2 case-control studies) were included, involving 1805697 participants. The detailed characteristics of included studies are shown in Table 1 and 2.

***Quantitative synthesis***

The main results are summarized in Table 3.

**Dietary cholesterol and the risk of pancreatic cancer:** For the highest versus 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:** Highest serum TC levels *vs* lowest levels were 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 RR for Europe and Asia 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.

***Sources of heterogeneity and sensitive 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](#_ENREF_26),[33](#_ENREF_33)] (RR > 3.0), the heterogeneity 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) and serum TC (*P* = 0.204).

**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 under power to detect the effect. Therefore, we conducted a meta-analysis to get a more reasonable conclusion. This meta-analysis, which 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 the association was significant 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](#_ENREF_37)]. Longstanding pre-existing chronic pancreatitis is a strong risk factor for pancreatic cancer[[40](#_ENREF_40)]. Moreover, dietary cholesterol may affect bile excretion. This may cause bile reflux into the head of the pancreas *via* the common duct, where most tumors occur[[26](#_ENREF_26),[41](#_ENREF_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 and 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 reduced to 49.7% and 0.0%, respectively. After excluding two studies[[26](#_ENREF_26),[33](#_ENREF_33)] (RR > 3.0) in the analysis for dietary cholesterol, the between-study heterogeneity reduced to 29.4%, and the result didn’t 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 reasonable conclusion. Second, almost all studies included in this meta-analysis 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](#_ENREF_26),[33](#_ENREF_33)] (RR > 3.0) in dietary cholesterol analysis, the between-study heterogeneity reduced to 29.4%, but the result didn’t change substantially.

However, the present study has a few 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 found not 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, except for European. 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, except for European.

***Applications***

The result 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, except for European.

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Study** | **Mean age (case/control) Percentage of male(case/control)** | **Sample** | **Cut-points for cholesterol**  | **Adjustment for covariates** |
| **(yr)** | **design** | **size** | **exposure RR (95%CI)** |
| 　 | 　 | **(cases)** | 　 |
| Lin Y *et al*[13] | Japan | case-control study | 64.7/65.1 | 327 | Dietary cholesterol exposure (mg), < 206(referent), 206-330, | Age and pack-years of smoking |
| -2005 | NA | -109 | > 330 [2.06(1.11-3.85)] |
| Chan JM | United States | case-control study | NA 54.7/51.9 | 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 |
| *et al*[14] | -2007 | -532 |
| Hu J *et al*[15] | Canada | case-control study | 61.6/57.1  | 5667 | Dietary cholesterol cut-point | 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 | (mg/week) < 966.261(referent), 966.262-1412.753, 1412.754-1880.265, |
|  |  |  | > 1880.266 [1.57(1.09-2.26)] |
| Howe GR | Metropolitan Toronto | case-control study | 64.6/64.8  | 754 | Mean difference per day | Caloric and fibre intake, lifetime cigarette consumption |
| *et al*[17] | -1990 | 56.6/53.5 | -249 | quartile 4-quartile 1 (569 mg) [0.95 (0.51-1.75)] |
| Bueno de | Netherlands | case-control study | NA 54.9/48.3 | 644 | Dietary cholesterol  | Age, sex, response status, total smoking and dietary intake of energy |
| Mesquita HB | -1991 | -164 | [1.33(0.72-2.45)] |
| *et al*[18] |  |  |  |
| Lucenteforte E | Italy | case-control study | NA 53.4/53.4 | 978 | First quintile of cholesterol exposure (referent),second *vs* first, | Year of interview, education, tobacco smoking, history of diabetes and total energy intake |
| *et al*[19] | -2010 | -326 | third *vs* first, fourth *vs* first,  |
| 　 | 　 | 　 | fifth *vs* first [1.10(0.68-1.77)] |
| Baghurst *et al*[26] | Australia | case-control study | NA 50.0/56.1 | 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 | -104 |
| Ghadirian *et al*[27] | Canada | case-control study | 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] | Netherlands | case-cohort study | NA 52.9/49.1 | 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 | -350 |
| Kalapothaki *et al*[29] | Greece | case-control study | NA 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 | -181 |
| Michaud *et al*[30] | United States | cohort | NA 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 | -178 |
| Nothlings *et al*[31] | Hawaii and Los Angeles | cohort | 65/60 51.2/45.3 | 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 | -482 |
| Stolzenberg-Solomon *et al*[32] | Finland | cohort | 58/57 | 27111 | First quintile of cholesterol exposure (referent),second *vs* first,  | Energy intake, age and years of smoking, energy-adjusted saturated fat intake |
| -2002 | NA | -163 | third *vs* first, fourth *vs* first,  |
|  |  |  | fifth *vs* first [0.92(0.53-1.59)] |
| Zatonski *et al*[33] | Poland | case-control study | 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 male (case/control)** | **Sample size** **(cases)** | **Cut-points for cholesterol** **Exposure RR (95% CI)** | **Adjustment for covariates** |
| Wu *et al*[16] | China(2012) | case-control study | 59.3/59.358.6/58.6 | 840(210) | Serum TC < 5.70mmol/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 study | NA | 29048(172) | Serum TC < 5.18mmol/L(referent),≥ 5.18mmol/L [0.88(0.60-1.28)] | Age, years smoked, cigarettes smoked per day, self-reported history of diabetes andbronchial asthma, occupational activity, measured high blood pressure |
| Johansen *et al*[21] | Austria, Norway, and Sweden(2010) | cohort study | 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 study | 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] | Korea(2011) | cohort study | 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] | Korea(2011) | cohort study | 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 study | 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 study | 61.4/60.7459.3/60.5 | 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.

**Table 3** **Pooled RR (95%CI) 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 1 Flow diagram of literature search**



**Figure 2 Forest plot of the relative risks with corresponding 95%CIs of studies on dietary cholesterol and pancreatic cancer.**



**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.**

