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ORIGINAL ARTICLE

Meta analysis of the association of cholesterol with pancreatic carcinoma risk

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Summary

Purpose: *Pancreatic carcinoma is a malignant tumor with poor prognosis. This metaanalysis was conducted to investigate if there exists any association of cholesterol with pancreatic carcinoma risk.*

Methods*: A literature search was performed in Cochrane Central Library, PubMed, MEDLINE, EMBASE, CNKI (China National Knowledge Infrastructure), China Biology Medical literature database (CBM), and WangFang database for relevant available articles. Dietary cholesterol and serum levels of total cholesterol (TC) were assessed and compared. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated.*

Results: *A total 19 articles coming from Europe, Asia and north America were assessed in this study. There was a significant difference between highest and lowest dietary cholesterol intake for pancreatic carcinoma risk (RR=1.31, 95% CI:1.10 to 1.56, p=0.01). Moreover, in subgroup analysis, there was a significant difference between highest and lowest dietary cholesterol intake for pancreatic carcinoma risk for case-control studies (RR=1.52, 95% CI:1.23 to 1.90, p=0.04). However, no significant difference was noticed between highest and lowest dietary cholesterol intake for pancreatic carcinoma risk for cohort studies (RR=1.02, 95% CI:0.87 to 1.20, p=0.51). The meta analysis results showed a significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma in Europeans (RR=1.15, 95% CI:0.86 to 1.53, p=0.05). Moreover, compared to the low serum level of TC, the high level serum TC was associated with pancreatic carcinoma risk (RR=1.00, 95% CI:0.86-1.17, p=0.03). There was a significant difference between high and low levels of serum TC for pancreatic carcinoma risk in Europeans (RR=1.03, 95% CI: 0.72 to 1.48, p=0.04).*

Conclusion: *Dietary or serum cholesterol may be associated with risk for increased pancreatic carcinoma.*

Key words: *cholesterol, meta-analysis, pancreatic carcinoma*

Introduction

Pancreatic carcinoma is one of the most lethal human gastrointestinal malignancies, constituting a major unsolved health problem. In Europe, pancreatic carcinoma is the 6th leading cause of cancer-related deaths [1]. The estimated numbers of cases and deaths of this malignancy were 277000 and 266000 respectively in 2008 worldwide [2]. Moreover, it was estimated that 43920 people would be diagnosed with pancreatic carcinoma and 37390 would die of this disease in 2012 [3]. However, the numbers of new pancreatic carcinoma cases and deaths expected in the United States were 46,420 and 39,590 respectively in 2014 [4].

The primary etiologic factors for pancreatic carcinoma are poorly understood. Research efforts aimed at quantifying risk factors and identifying individuals at high risk for pancreatic cancer development are critical for realizing a strategy for the prevention of this diseases. Recently, it has been reported that several factors are associated with pancreatic carcinoma, including age [5], diet and tobacco smoking [6], body mass index (BMI) [7], and family history [8]. Moreover, cholesterol appeared to have an influence on pancreatic carcinoma risk [9-12].

The development of new and potent treatment options is strongly needed. Several epide-

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miologic studies have revealed that dietary cholesterol was associated with increased pancreatic carcinoma risk [9,11,12]. However, others studies demonstrated no association of cholesterol with pancreatic carcinoma risk [13-15]. The association between serum total cholesterol (TC) and pancreatic carcinoma risk also remains inconsistent [16].

In this study we present the results of a meta analysis performed to reveal possible association of cholesterol with pancreatic carcinoma risk, which might be useful to enlighten the dispute over this topic.

Methods

Search strategy

We searched the Cochrane Central Library, PubMed, MEDLINE, EMBASE, CNKI (China National Knowledge Infrastructure), China Biology Medical literature database (CBM), and WangFang database up to July 2014. The search terms were as follows: "pancreatic cancer", "pancreatic carcinoma", "pancreatic neoplasm" "pancreatic tumor", "cholesterol". The search was limited to studies in humans. Titles and abstracts of all citations were screened independently by two reviewers. The outcomes focused on the association of dietary cholesterol and serum TC with pancreatic carcinoma risk. No language restrictions were applied.

Data extraction

Two reviewers independently extracted the following parameters from each study: general information, information on participants, baseline characteristics of included studies and outcomes. Discrepancies between the two reviewers were resolved by discussion and consensus.

Statistics

For data analysis we used the STATA software, version 13.0 (Stata Corporation, College Station, TX, USA). The association of dietary cholesterol intake or serum TC level with pancreatic cancer risk between pancreatic carcinoma patients and a healthy control group (no pancreatic or other carcinomas) was evaluated. The RR value represented the relative risk of cancer risk in the pancreatic carcinoma group compared with the healthy control group. A p value <0.05 was considered as statistically significant. Quantification of the heterogeneity effect was assessed by means of I square (I^2) test. We considered heterogeneity to be present if the I^2 statistics was >50%. Funnel plots and Egger test were adopted to evaluate publication bias. Possible sources of heterogeneity were assessed by subgroup, sensitivity and meta-regression analyses. A p value<0.05 was considered as statistically significant.

Results

Study characteristics

A total of 19 articles [9-27] including 439355 participants for the association of dietary cholesterol with pancreatic carcinoma and 1805697 participants for the association of serum TC with

Table 1. General data of studies for dietary cholesterol

First author [Ref]	*Country (year)*	*Study design*	*Mean age (case/control, years)*	*Percent of males (case/control, %)*	*Sample size (cases)*
Baghurst et al [17]	Australia (1991)	case-control	-	50.0/56.1	357 (104)
Bueno de Mesquita et al [13]	Netherlands (1991)	case-control	-	54.9/48.3	644 (164)
Chan et al [12]	US (2007)	case-control	-	54.7/51.9	2233 (532)
Ghadirian et al [22]	Canada (1995)	case-control	63.9/62.1	54.2/51.5	418 (179)
Heinen et al [23]	Netherlands (2009)	case-cohort	-	52.9/49.1	120852 (350)
Howe et al [14]	Canada (1990)	case-control	64.6/64.8	56.6/53.5	754 (249)
Hu et al [11]	Canada (2012)	case-control	61.6/57.1	56.2/50.5	5667 (628)
Kalapothaki et al [24]	Greece (1993)	case-control	-	-	362 (181)
Lin et al [9]	Japan (2005)	case-control	64.7/65.1	-	327 (109)
Lucenteforte et al [15]	Italy (2010)	case-control	-	53.4/53.4	978 (326)
Michaud et al [18]	US (2003)	cohort	-	-	88802 (178)
Nothlings et al [19]	US (2005)	cohort	65/60	51.2/45.3	190545 (482)
Stolzenberg-Solomon et al [20]	Finland (2002)	cohort	58/57	-	27111 (163)
Zatonski et al [21]	Poland (1991)	case-control	62.2/63.2	61.8/45.6	305 (110)

-: not available

Table 2. General data of studies for serum total cholesterol

First author [Ref]	*Country (year)*	*Study design*	*Mean age (case/control, years)*	*Percent of males (case/control, %)*	*Sample size (cases)*
Johansen et al [16]	Austria, Norway, and Sweden (2010)	cohort	-	-	289866 (543)
Johansen et al [16]	Austria, Norway, and Sweden (2010)	cohort	-	-	288834 (314)
Kitahara et al [27]	Korea (2011)	cohort	-	-	756604 (1799)
Kitahara et al [27]	Korea (2011)	cohort	-	-	433115 (776)
Kuzmickiene et al [25]	Lithuania (2013)	cohort	-	-	6788 (73)
Stolzenberg-Solomon et al [19]	Finland (2002)	cohort	58/57	-	29048 (172)
Wu et al [10]	China (2012)	case-control	59.3/59.3	58.6/58.6	840 (210)
Xu et al [26]	China (2011)	case-control	61.4/60.74	59.3/60.5	602 (290)

-: not available

Table 3. Associations of dietary cholesterol and serum total cholesterol with pancreatic cancer risk

Cholesterol source	*Subgroup*	*No. of studies*	*RR (95%CI)*	*I^2 (%)*	*p value*
Dietary cholesterol	All studies	14	1.31 (1.10-1.56)	55.3	0.01
	Case-control	10	1.52 (1.23-1.90)	49.7	0.04
	Cohort	4	1.02 (0.87-1.20)	0.0	0.51
Continent	North America	6	1.28 (1.06-1.54)	29.3	0.22
	Europe	6	1.15 (0.86-1.53)	55.4	0.05
	Asia	2	2.50 (1.57-3.98)	0.0	0.36
Serum total cholesterol	All studies	8	1.00 (0.86-1.17)	55.5	0.03
Continent	Asia	4	1.01 (0.85-1.19)	56.2	0.08
	Europe	4	1.03 (0.72-1.48)	65.1	0.04

pancreatic carcinoma were included into this meta analysis. The year of publication of the studies included ranged from 1990 to 2014. More detailed characteristics of the included papers are shown in Tables 1 and 2.

Association of dietary cholesterol with pancreatic carcinoma risk

As shown in Table 3, there was a significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma risk (RR=1.31, 95% CI:1.10 to 1.56, p=0.01). Moreover, for case-control studies, there was also a significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma risk (RR=1.52, 95% CI:1.23 to 1.90, p=0.04). However, no significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma risk was noticed in cohort studies (RR=1.02, 95% CI:0.87 to 1.20, p=0.51).

For different geographic areas there were different results. In Europe, the results showed a significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma risk (RR=1.15, 95% CI:0.86 to 1.53, p=0.05), yet, no significant differences were observed between highest and lowest dietary cholesterol for pancreatic carcinoma risk in North America and Asia (RR=1.28, 95% CI:1.06 to 1.54, p=0.22; RR=2.50, 95% CI:1.57 to 3.98, p=0.36), respectively.

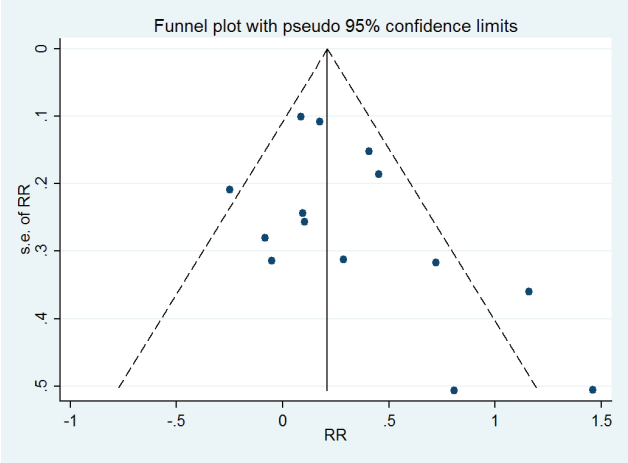

Figure 1. Funnel plots and Egger test demonstrating no publication bias between dietary cholesterol or serum total cholesterol and pancreatic carcinoma risk.

Relationship between serum TC and pancreatic carcinoma risk

As shown in Table 3, there was a significant difference concerning the association of high level of serum TC with pancreatic carcinoma risk compared with low level of serum TC (RR=1.00, 95% CI:0.86-1.17, p=0.03). For different geographic areas, there was significant difference between higher and lower serum TC for pancreatic carcinoma risk in Europe (RR=1.03, 95% CI: 0.72 to 1.48, p=0.04) compared to Asia (RR=1.01, 95% CI:0.85 to 1.12, p=0.08).

Publication bias

As shown in Figure 1, the funnel plots and Egger test demonstrated no publication bias between dietary cholesterol or serum TC and pancreatic carcinoma risk.

Discussion

In this meta analysis we tried to investigate the association of cholesterol with pancreatic carcinoma risk. The results showed that there was a significant difference between highest and lowest dietary cholesterol for pancreatic carcinoma risk. Significant differences were observed between highest dietary cholesterol with pancreatic carcinoma risk compared with lowest dietary cholesterol in Europe. Meanwhile, there was a significant difference on the association of high level vs low level of serum TC with pancreatic carcinoma risk. Compared to the lower serum TC, there was an even more higher level of serum TC in pancreatic carcinoma patients in Europe.

Several underlying mechanisms have been proposed to investigate the relationship between cholesterol and pancreatic carcinoma risk. Recently, a new study has shown that reduction of cholesterol synthesis inhibits the pancreatic carcinoma growth [28]. Another study has also found that cholesterol increases tumor growth and carcinogenic activity in breast cancer [29]. Souchek et al. [30] reported that inhibition of cholesterol biosynthesis can increase the radiosensitivity in pancreatic carcinoma patients. In lung cancer, a newest study has shown that cholesterol oxidase can promote cancer cells' apoptosis by cholesterol oxidation [31].

In the present meta analysis, a large number of participants was included, something that provides a greater possibility of reaching a reasonable conclusion. However, the present study has a few limitations, such as exaggerating or underestimating the risk due to some unknown confounders not being excluded from the studied papers. Moreover, significant differences were found concerning the association of dietary cholesterol with pancreatic carcinoma risk in different geographical areas, which shows the need for more data in future analyses over this topic.

In conclusion, our meta analysis revealed that dietary or serum cholesterol may be associated with increased pancreatic carcinoma risk, which provides a foundation of pancreatic carcinoma. However, more studies should be included into meta analyses in the future.

References

1. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chirurgica 2004;59:99-111.
2. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-2917.
3. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. CA Cancer J Clin 2012;62:10-29.
4. Siegel R, Ma J, Zou Z et al. Cancer Statistics, 2014. CA Cancer J Clin 2014;64:9-29.
5. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol 2006;20:197-209.
6. Jarosz M, Sekuła W, Rychlik E. Influence of diet and tobacco smoking on pancreatic cancer incidence in Poland in 1960-2008. Gastroenterol Res Pract 2012;2012:682156.
7. Bethea TN, Kitahara CM, Sonderman J et al.A pooled analysis of body mass index and pancreatic cancer mortality in African Americans. Cancer Epidemiol Biomarkers Prev 2014 Jul 13;23:2119-2125.
8. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Famil Cancer 2009;8:109-117.
9. Lin Y, Tamakoshi A, Hayakawa T et al. Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan. J Gastroenterol 2005;40:297-301.
10. Wu Q, Chen G, Wu WM et al. Metabolic syndrome components and risk factors for pancreatic adenocarcinoma: a case-control study in China. Digestion 2012;86:294-301.
11. Hu J, La Vecchia C, de Groh M et al. Canadian Cancer Registries Epidemiology Research G. Dietary cholesterol intake and cancer. Ann Oncol 2012;23:491-500.
12. Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. Cancer Causes Control 2007;18:1153-1167.
13. Bueno de Mesquita HB, Maisonneuve P, Runia S et al. Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in The Netherlands. Int J Cancer 1991;48:540-549.
14. Howe GR, Jain M, Miller AB. Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case-control study. Int J Cancer 1990;45:604-608.
15. Lucenteforte E, Talamini R, Bosetti C et al. Macronutrients, fatty acids, cholesterol and pancreatic cancer. Eur J Cancer 2010;46:581-587.
16. Johansen D, Stocks T, Jonsson H et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. Cancer Epidemiol Biomarkers Prev 2010;19:2307-2317.
17. Baghurst PA, McMichael AJ, Slavotinek AH et al. A case-control study of diet and cancer of the pancreas. Am J Epidemiol 1991;134:167-179.
18. Michaud DS, Giovannucci E, Willett WC et al. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol 2003;157:1115-1125.
19. Nothlings U, Wilkens LR, Murphy SP et al. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst 2005;97:1458-1465.
20. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR et al. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol 2002;155:783-792.
21. Zatonski W, Przewozniak K, Howe GR et al. Nutritional factors and pancreatic cancer: a case-control study from south-west Poland. Int J Cancer 1991;48:390-394.
22. Ghadirian P, Baillargeon J, Simard A et al. Food habits and pancreatic cancer: a case-control study of the Francophone community in Montreal, Canada. Cancer Epidemiol Biomarkers Prev 1995;4:895-899.
23. Heinen MM, Verhage BA, Goldbohm RA et al. Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. Int J Cancer 2009;125:1118-1126.
24. Kalapothaki V, Tzonou A, Hsieh CC et al. Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece. Cancer Causes Control 1993;4:383-389.
25. Kuzmickiene I, Everatt R, Virviciute D et al. Smoking and other risk factors for pancreatic cancer: a cohort study in men in Lithuania. Cancer Epidemiol 2013;37:133-139.
26. Xu P, Huang Q, Liu CH et al. Risk factors for pancreatic cancer: a case-control study. Tumori 2011;31:653-657.
27. Kitahara CM, Berrington de Gonzalez A, Freedman ND et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29:1592-1598.
28. Cantoria MJ, Boros LG, Meuillet EJ. Contextual inhibition of fatty acid synthesis by metformin involves glucose-derived acetyl-CoA and cholesterol in pancreatic tumor cells. Metabolomics 2014;10:91-104.
29. Poirot M, Silvente-Poirot S. Cholesterol-5,6-epoxides: chemistry, biochemistry, metabolic fate and cancer. Biochimie 2013;95:622-631.
30. Souchek JJ, Baine MJ, Lin C et al.Unbiased analysis of pancreatic cancer radiation resistance reveals cholesterol biosynthesis as a novel target for radiosensitization. Br J Cancer 2014;111:1139-1149.
31. Liu J, Xian G, Li M et al. Cholesterol oxidase from Bordetella species promotes irreversible cell apoptosis in lung adenocarcinoma by cholesterol oxidation. Cell Death Dis 2014;5:e1372.