RESEARCH ARTICLE

Association Between Pancreatitis and Subsequent Risk of Pancreatic Cancer: a Systematic Review of Epidemiological Studies

Gui-Xian Tong[&], Qing-Qing Geng[&], Jing Chai, Jing Cheng, Peng-Lai Chen, Han Liang, Xing-Rong Shen, De-Bin Wang*

Abstract

This study aimed to summarize published epidemiological evidence for the relationship between pancreatitis and subsequent risk of pancreatic cancer (PC). We searched Medline and Embase for epidemiological studies published by February 5th, 2014 examining the risk of PC in pancreatitis patients using highly inclusive algorithms. Information about first author, year of publication, country of study, recruitment period, type of pancreatitis, study design, sample size, source of controls and attained age of subjects were extracted by two researchers and Stata 11.0 was used to perform the statistical analyses and examine publication bias. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with the random effects model. A total of 17 articles documenting 3 cohort and 14 case-control studies containing 14,667 PC cases and 17,587 pancreatitis cases were included in this study. The pooled OR between pancreatitis and PC risk was 7.05 (95%CI: 6.42-7.75). Howeever, the pooled ORs of case-control and cohort studies were 4.62 (95%CI: 4.08-5.22) and 16.3 (95%CI: 14.3-18.6) respectively. The risk of PC was the highest in patients with chronic pancreatitis (pooled OR=10.35; 95%CI: 9.13-11.75), followed by unspecified type of pancreatitis (pooled OR=6.41; 95%CI: 4.93-8.34), both acute and chronic pancreatitis (pooled OR=6.13; 95%CI: 5.00-7.52), and acute pancreatitis (pooled OR=2.12; 95%CI: 1.59-2.83). The pooled OR of PC in pancreatitis cases diagnosed within 1 year was the highest (pooled OR=23.3; 95%CI: 14.0-38.9); and the risk in subjects diagnosed with pancreatitis for no less than 2, 5 and 10 years were 3.03 (95%CI: 2.41-3.81), 2.82 (95%CI: 2.12-3.76) and 2.25 (95%CI: 1.59-3.19) respectively. Pancreatitis, especially chronic pancreatitis, was associated with a significantly increased risk of PC; and the risk decreased with increasing duration since diagnosis of pancreatitis.

Keywords: Pancreatitis - pancreatic cancer - risk factor

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Introduction

Pancreatic cancer (PC) has become one of the most serious diseases threatening human health and life all over the world. GLOBOCAN 2008 reported that there were about 277 thousand new PC cases (including 144 thousand males and 133 thousand females) and 266 thousand PC deaths (including 138 thousand males and 127 thousand females) worldwide (Ferlay et al., 2010). Although PC is less common than cancer of the lung, breast, colorectum, stomach and liver, etc., only ranked thirteenth (accounted for only 2.2%) of all new cancer cases; its mortality rate is quite high, ranked eighth (accounted for 3.5%) of all cancer deaths. Pancreatic ductal adenocarcinoma, the most common type of PC, was the fourth leading cause of cancer death in the United States with a median survival of <6 month and a 5-year survival rate less that 5% (Hezel et al., 2006). It is believed that risk factors of PC could be divided into 2 categories including environmental factors (e.g., cigarette smoking, alcohol drinking, coffee intake, diabetic mellitus, cholelithiasis, H. pylor infection) and genetic factors (e.g., family history of PC and high expression of BRCA2). Of these, cigarette smoking has been regarded as the most important risk factor. Smokers have 2-fold to 3-fold increased risk of PC compared to non-smokers with cigarette smoking accounting for approximately a quarter of PC incidence (Howe et al., 1991; Silverman et al., 1994; Fuchs et al., 1996; Lowenfels et al., 2006; Ko et al., 2007; Bao et al., 2009; Talamini et al., 2010; Nitsche et al., 2011). Hereditary PC accounts for 5%-10% of all cases. Individuals with family history of PC, especially have first-degree relative(s) with PC, were consistently been found to be associated with added risk, and risk raised as the number of affected first-degree relative increased (Falk et al., 1998; Brentnall et al., 1999; Klein et al., 2004; Ko et al., 2007; Permuth-Wey et al.,

Center for Health Management, School of Health Services Management, Anhui Medical University , Hefei, China [&]Equal contributors
**For correspondence: dbwang@vip.sina.com*

2009).

The associations between medical conditions and the risk of PC have been explored extensively for the past several decades. Of these, pancreatitis (including its acute and chronic forms) is one of the most frequently studied diseases. Although the pathogenesis mechanisms underlying the role of pancreatitis in PC etiology are still unclear, the molecular pathway for this association had been put forward by several hypotheses (Sakorafas et al., 2012; Gukovsky et al., 2013; Pinho et al., 2014; Kolodecik et al., 2014). Just like other benign diseases are associated with an increased cancer risk in the target organs (e.g., hepatitis and liver cancer, gastritis and gastric cancer), increased cell turnover and defective DNA repair in pancreatitis cases could lead to the occurrence of PC. Rosty and colleagues found a significant minority of pancreatic intraepithelial lesions (PanINs) arising in chronic pancreatitis cases showed loss of p16 expression (Rosty et al., 2003), a common precursor of cancer (Lowenfels et al., 2006). A meta-analysis of 15 studies documented that K-ras mutations, which play an important role in the evolution of PC, had been detected in subjects with chronic pancreatitis (Löhr et al., 2005). Past decades witnessed a variety of epidemiological studies on this issue, those including case-control, retrospective cohort and prospective cohort studies of patients affected by pancreatitis (Lowenfels et al., 1993; Malka et al., 2002). A meta-analysis published in 2010 documented a 5.1-fold risk of developing PC in patients with unspecified pancreatitis, 13.3-fold in patients with chronic pancreatitis and 69.9-fold risk for hereditary pancreatitis (Raimondi et al., 2010). In recent years, several new and large sample size studies conducted in Australia, China, Canada, Europe and United States, Denmark and Taiwan have been published. Thus, an updated comprehensive assessment may provide more accurate and detailed information. This study aims at summarizing published epidemiological evidence and producing an updated pooled evidence of relationship between pancreatitis and PC.

Materials and Methods

Data sources and search strategy

We utilized two approaches to locate as many relevant papers as possible. First, we searched the literatures in Medline and Embase available by February 5th, 2014 using the following search terms "(pancreatitis) AND (cancer OR neoplasm* OR tumour OR tumor OR carcinoma OR malignanc* OR adenocarcinoma) AND (pancreatic OR pancreas)", where * represents wildcard characters. Second, we reviewed the bibliographies of relevant review papers for additional articles. This process was conducted iteratively until no new papers were identified.

Inclusion criteria

The inclusion criteria of were paper: 1) written in English; 2) cohort or case-control study investigating the relationships between PC and medical conditions that include pancreatitis; and 3) provided adequate original data for the recalculation of odds ratio (OR) or relative risk (RR) of PC.

Data extraction and analysis

Descriptive data about the included studies were extracted from the papers identified using a data-extracting form, comprising first author, year of publication, country of study, recruitment period, type of pancreatitis, study design, sample size, source of controls and attained age of subjects (the age of subjects when they were studied). All data were extracted independently by two researchers and discrepancies were solved by consensus. Stata 11.0 (StataCorp, College Station, TX, USA) was used to perform statistical analyses and examine publication bias. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random effects model.

Quality assessment

Newcastle-Ottawa Scale (NOS) (Wells et al., 2011) was used to assess the methodological quality of included studies. The tool provides a comprehensive score system with 8 items for both case-control and cohort studies. Quality items of case-control studies include adequate definition of patient cases (0-1 point), representativeness of patients cases (0-1 point), selection of controls (0-1 point), definition of controls (0-1 point); comparison controlled for important factor or additional factor (0-2 point), ascertainment of exposure (0-1 point), same method of ascertainment for participants (0-1 point) and non-response rate (0-1 point); while quality items of cohort studies include representativeness of the exposed cohort (0-1 point), selection of the non-exposed cohort (0-1 point), ascertainment of exposure (0-1 point), outcome of interest not presented at start of study (0-1 point), comparison based on the design or analysis (0-2 point), assessment of outcome (0-1 point), long enough follow-up for outcomes to occur (0-1 point) and adequate evaluation of follow-up of cohorts (0-1 point). Total score was calculated by adding up the points awarded to each item. Only studies scored 6 or higher were considered to be of high methodological quality.

Results

Studies included

A total of 11563 articles were retrieved from Medline and Embase, of which 10507 articles were excluded on the basis of title and abstract. Of the remaining 51 articles, 43 were excluded after more detailed evaluation via full texts including 17 articles with irrelevant contents, 6 review articles, 13 studies without control group and 7 papers lacking original data for further analysis. After combining the 4 studies from reference lists, 17 studies finally met the inclusion criteria and included in this study (Figure 1).

Descriptive analyses

As shown in Table 1, the 17 articles documented 3 cohort and 14 case-control studies containing 14667 PC cases and 17587 pancreatitis cases from countries of Australia, Canada, China, Denmark, Finland, Greece, Italy, Netherlands, Poland and United States etc. The sample sizes of studies ranged from 218 to 779430 and the mean/median attained age of subjects ranged from

54.5 to 66.1. Nine out of the 17 studies did not specify the type of pancreatitis; four studies included both acute and chronic pancreatitis and the remaining four, limited to chronic pancreatitis. Source of controls varied across studies including community population (n=10), hospital patients (n=3), visiting relatives of hospital patients (n=1), hospital patients and community population (n=1), hospital patients and visiting relatives of hospital patients (n=1), and visiting relatives of hospital patients and community population (n=1).

Pancreatitis and PC

The ORs of included studies ranged from 1.68(95% CI: 0.62-4.54) to 18.52 (95% CI: 16.00-21.42) with a pooled OR of 7.05 (95% CI: 6.42-7.75), and the heterogeneity was quite high (I2 =94.7%, P<0.001). Subgroup analysis revealed pooled ORs of case-control and cohort designed studies as 4.62 (95% CI: 4.08-5.22) and 16.31 (95% CI: 14.30-18.61) respectively (Figure 2). As shown in Figure 3, the risk of PC was highest in patients with chronic pancreatitis (pooled OR=10.35; 95% CI: 9.13-11.75), followed by unspecified type of pancreatitis (pooled OR=6.41; 95% CI: 4.93-8.34), both acute and chronic pancreatitis (pooled OR=6.13; 95% CI: 5.00-7.52), and acute pancreatitis (pooled OR=2.12; 95% CI: 1.59-2.83). Figure 4 reveals that the risks of PC were inconsistent among subjects with different duration since diagnosis of pancreatitis. The risk of PC was the highest in pancreatitis cases diagnosed within 1 year with a pooled OR of 23.30 (95% CI: 13.95-38.93). And the risk decreased significantly as duration since diagnosis of pancreatitis increased. The pooled ORs of PC were 3.03 (95% CI: 2.41-3.81), 2.82 (95% CI: 2.12-3.76) and 2.25 (95% CI: 1.59-3.19) in individuals diagnosed with pancreatitis for

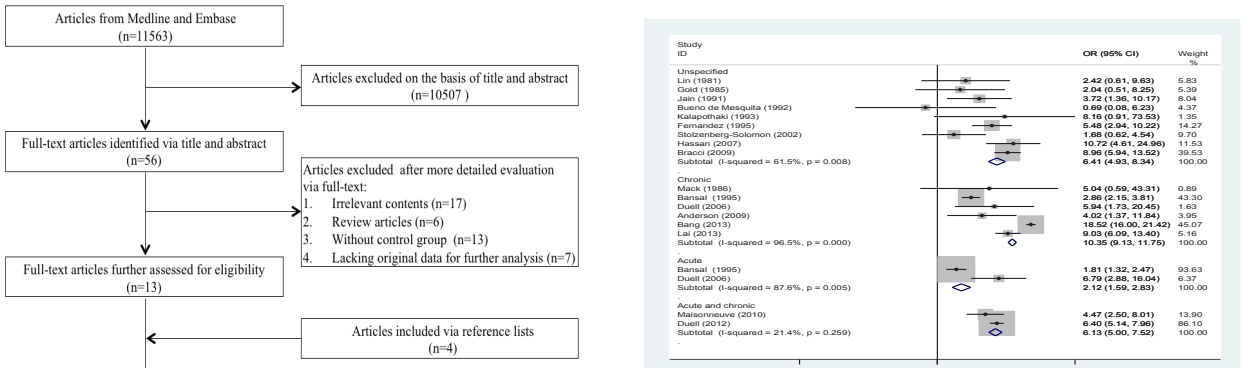

Figure 1. Flow Diagram of Study Selection Process

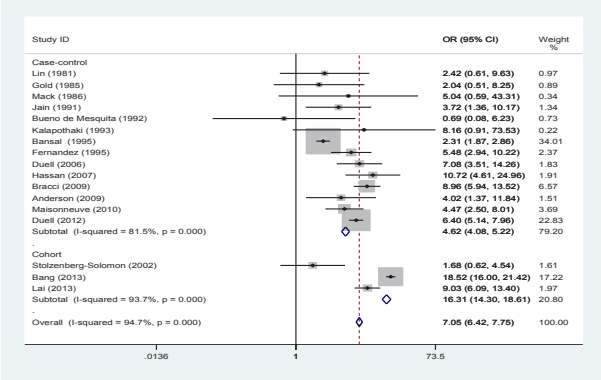

Figure 2. Forest Plot of ORs between Pancreatitis and Pancreatic Cancer

Figure 3. Forest Plot of ORs between Pancreatitis and Pancreatic Cancer Stratified by type of Pancreatitis

Table 1. Characteristics of Studies

First author & publication year	Location & recruitment period	Type of pancreatitis	Cancer cases/ pancreatitis cases	Source of controls	Attained age of subjects
Case-control studies					
Lin 1981	United States (1972-1975)	Unspecified	109/10	Hospital patients	15 to ≥85
Gold 1985	United States (1978-1980)	Unspecified	199/8	Hospital patients, population	Mean age of cancer cases=66.1
Mack 1986	United States (1976-1981)	Chronic	490/6	Population	<50 to ≥60
Jain 1991	Canada (1983-1986)	Unspecified	260/17	Population	Mean age=64.7
Bueno de Mesquita 1992	Netherlands (1984-1987)	Unspecified	177/5	Population	35 to 79
Kalapothaki 1993	Greece (1991-1992)	Unspecified	181/5	Hospital patients, hospital visitors	≤50 to ≥80
Bansal 1995	United States (1988-1992)	Acute, chronic	2639/364	Hospital patients	NA
Fernandez 1995	Italy (1983-1992)	Unspecified	362/42	Hospital patients	<45 to 74
Duell 2006	United States (1994-2005)	Acute, chronic	308/37	Population	21-85
Hassan 2007	United States (2000-2006)	Unspecified	808/66	Hospital visitors	Mean age=61.1
Bracci 2009	United States (1995-2006)	Unspecified	1659/165	Hospital visitors, population	<50 to ≥80
Anderson 2009	Canada (2003-2007)	Chronic	419/25	Population	Mean age=64.3
Maisonneuve 2010	Australia, Canada, Netherlands and Poland (1983-1988)	Acute, chronic	823/53	Population	<40 to>80
Duell 2012	Australia, China, Canada, Europe and United States (1983-2009)	Acute, chronic	4987/425	Population	<50 to ≥75
Cohort studies					
Stolzenberg-Solomon 2002	Finland (1985-1988)	Unspecified	172/408	Population	53 to 62 (mean age=57)
Bang 2013	Denmark (1995-2000)	Chronic	797/11972	Population	45 to 64 (median age=54.5)
Lai 2013	Taiwan (2000-2003)	Chronic	585/4016	Population	<45 to ≥65

Table 2. Quality of Included Studies Based on the Newcastle-Ottawa Scale

First author & year		Selection (score)					Comparability (score)		Exposure (score)			Total Score
		Adequate definition of patient cases	Representativeness of patients cases	Selection of controls	Definition of controls	Outcome of interest was not present at start of study	Control for important factor or additional factor	Based on the design or analysis	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate	
Case-control studies	Lin 1981	1	1	0	1		1		0	1	0	5
	Gold 1985	1	1	1	1		2		0	1	0	7
	Mack 1986	1	1	1	1		2		0	1	0	7
	Jain 1991	1	1	1	1		2		0	1	0	7
	Bueno de Mesquita 1992	1	1	1	1		2		0	1	0	7
	Kalapothaki 1993	1	1	0	1		1		0	1	0	5
	Bansal 1995	1	1	1	1		2		1	1	0	8
	Fernandez 1995	1	1	0	1		1		0	1	0	5
	Duell 2006	1	1	1	1		2		0	1	0	7
	Hassan 2007	1	1	1	1		2		0	1	0	7
	Bracci 2009	1	1	1	1		2		0	1	1	8
	Anderson 2009	1	1	1	1		2		1	1	0	8
	Maisonneuve 2010	1	1	1	1		2		0	1	0	7
	Duell 2012	1	1	1	1		2		0	1	0	7
First author & year		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study		Based on the design or analysis		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Cohort studies	Stolzenberg-Solomon 2002	1	1	1	1		1		1	1	1	8
	Bang 2013	1	1	1	1		2		1	1	1	9
	Lai 2013	1	1	1	1		2		1	1	1	9

Figure 4. Forest Plot of ORs between Pancreatitis and Pancreatic Cancer Stratified by Duration since Diagnosis of Pancreatitis

no less than 2, 5 and 10 years respectively.

Certain medical conditions influenced the association between pancreatitis and PC. Lai and colleagues' Taiwanese population-based cohort study revealed that chronic pancreatitis cases with diabetes mellitus had 2-fold higher risk than chronic pancreatitis without the disease; while patients with concurrent gallstones and chronic pancreatitis had a reduced risk compared with non-gallstones pancreatitis cases (Lai et al., 2013). A case-control study carried out in the United States showed that cases with history of pancreatitis had 7.2-fold excess risk of PC compared with non-pancreatitis history cases, while the risk decreased to 4.1 (95% CI: 2.0-108.0) in those had a history of both pancreatitis and gallbladder diseases (Bracci et al., 2009).

Quality of studies and Sensitivity analysis

As shown in Table 2, the total quality scores of studies ranged from 5 to 9 with a mean score of 7.12. Quality of cohort studies was relatively better compared with case-control studies. In case-control studies, only 2 studies ascertained blinding of diagnosis of pancreatitis, and only 1 studies made it clear that the difference in non-response rate was not statistically significant ($p > 0.05$) in both groups. After excluding 3 studies scored less than 6, the pooled OR increased slightly from 7.05 (95% CI: 6.42-7.75) to 7.13 (95% CI: 6.48-7.85).

Publication bias

A funnel plot was produced to detect the presence of publication bias and which revealed a relatively moderate degree of asymmetry. Begg's regression asymmetry test produced a p value of 0.171, indicating a low probability of publication bias.

Discussion

Our study revealed that pancreatitis, especially chronic pancreatitis, was associated with a significantly increased risk of PC compared with non-pancreatitis (the pooled ORs of overall and chronic pancreatitis was 7.05 and 10.35 respectively). This is consistent with the results

of a previous meta-analysis, which documented a relative risk of 13.3 (95% CI: 6.1-28.9) in patients with chronic pancreatitis (Raimondi et al., 2010). Our study also found that the risk of PC was the highest in pancreatitis cases diagnosed within 1 year (OR=23.30; 95% CI: 13.95-38.93), and the risk of PC declined as duration since diagnosis of pancreatitis increased, though remained elevated compared with non-pancreatitis. These results should be interpreted with caution for the following reasons: a) most of the included studies used case-control design which are subject to some extent of recall bias because PC patients may be more likely to report a past history of pancreatitis than control subjects (Fernandez et al., 1995; Lowenfels et al., 2006); b) only a few cases with past diagnosis of pancreatitis were observed in several small sample size studies, which did not prevent chance-finding; and c) inadequate data did not allow for rigorous analysis distinguishing associations with PC due to pancreatitis effect from that due to the presence of certain confounding risk factors (e.g., excessive alcohol and heavy smoking).

Compared with acute and chronic pancreatitis, certain rare types of pancreatitis seemed to be more closely associated with PC. Lowenfels and colleagues' cohort study of 412 hereditary pancreatitis patients in the United States showed that the risk of PC was approximately 50 to 60 times greater than background population (Lowenfels et al., 2000). A cohort study of 418 hereditary pancreatitis cases from 14 European countries revealed that the cumulative risk of PC was 44.0% (95% CI: 8.0%-80.0%) at 70 years from symptom onset, and the standardized incidence ratio reached 67.0% (95% CI: 50.0%-82.0%) (Howes et al., 2004). A recent published study of France cohort documented that the relative risk of PC for the whole population, men, and women were 87.0 (95% CI: 42.0-113.0), 69.0 (95% CI: 25.0-150.0), and 142.0 (95% CI: 38.0-225.0), respectively (Rebours et al., 2008). Chari and colleagues' study reported that subjects with tropical pancreatitis, a form of pancreatitis found primarily in southern Indian and in parts of sub-Saharan Africa, appeared to have a significantly increased risk of PC when compared with the background pancreatic cancer rate with an RR of 100.0 (95% CI: 37.0-218.0) (Chari et al., 1994).

Evidences regarding the associations between PC and other medical conditions were summarized in previous papers. Ben and colleagues performed a meta-analysis of cohort studies investigating the relationship between diabetes and PC and found that diabetes was associated with an increased risk of PC with a pooled RR of 1.94 (95% CI: 1.66-2.27) (Ben et al., 2011). Li's meta-analysis suggested that chronic hepatitis B virus infection was linked with increased risk of PC; the pooled OR of PC for overall, case-control and cohort studies were 1.40 (95% CI: 1.14-1.73), 1.43 (95% CI: 1.06-1.94) and 1.31 (95% CI: 1.00-1.72) respectively (Li et al., 2013). Recently published meta-analysis also found that cholecystectomy and gastrectomy were associated with 23% and 54% excess risk of PC respectively (Lin et al., 2012; Gong et al., 2012). While Olson et al' s pooled analysis of 10 case-control studies revealed that allergy was associated with reduced risk of PC with the pooled ORs of 0.79 (95% CI: 0.62-1.00) for all types of allergy, 0.74 (95% CI: 0.56-0.96) for hay fever and 0.62 (95% CI: 0.41-0.94) for allergy to animals (Olson et al., 2013).

Although there is a strong link between pancreatitis and PC, screening is not recommended for subjects with pancreatitis for the long time lag between the diagnosis of benign diseases and the occurrence of cancer. Future studies should focus on strategies using pancreatitis as an alarm sign and finding additional indications including medical conditions (e.g., diabetes mellitus, cholelithiasis and obesity), risk behaviors (cigarette smoking, alcohol drinking and coffee intake) and family history (e.g., first-degree relatives with PC) etc; and perform more sophisticated analysis of the risk of multi-indications or build multi-variable models (e.g., score systems, regression models). Future researchers should also have the vision and courage in conducting long-term, large sample size prospective cohort studies with adequate attention being paid to the study quality.

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