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). However, 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
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; Kolodeckik 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 cases diagnosed within 1 year with a pooled OR of 8.96 (5.94, 13.52) 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 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 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 cases diagnosed within 1 year with a pooled OR of 8.96 (5.94, 13.52) 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 acute pancreatitis (pooled OR=2.12; 95% CI: 1.59-2.83).

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

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<th>Selection of controls</th>
<th>Definition of controls</th>
<th>Control for important factor or additional factor</th>
<th>Ascertainment of exposure (blinding)</th>
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Discussion

Our study revealed that pancreatitis, especially chronic pancreatitis, was associated with a significantly increased risk of PC compared with non-pancreatitis. The pooled OR of overall case-control studies was 7.05 (95% CI: 2.0-22.9) and chronic pancreatitis was 7.12 (95% CI: 2.0-25.0). A funnel plot was produced to detect the presence of publication bias, and which revealed a relatively moderate degree of asymmetry. Begg's regression test produced a p value of 0.171, indicating a low probability of publication bias.

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

This is consistent with the results of previous studies. For example, a case-control study carried out in the United States showed that cases with a history of chronic pancreatitis had a 7.2-fold excess risk of PC compared with non-pancreatitis history cases. However, the risk decreased to 3.5 (95% CI: 2.0-6.6) in those with a history of chronic pancreatitis and gallbladder diseases (Bracci et al., 2009).

As shown in Table 2, the overall quality score was relatively moderate, with a mean score of 7.12. Quality of cohort studies was relatively better compared with case-control studies. The association between pancreatitis and PC was strong in the Taiwanese population-based cohort study (Lai et al., 2013). A case-control study carried out in the United States showed that cases with a history of chronic pancreatitis had a 7.2-fold excess risk of PC compared with non-pancreatitis history cases. However, the risk decreased to 3.5 (95% CI: 2.0-6.6) in those with a history of chronic pancreatitis and gallbladder diseases (Bracci et al., 2009).

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 compared with non-diabetes cases, while patients with concurrent gallstones and diabetes mellitus had 2.5-fold higher risk compared with non-diabetes cases. The risk was not statistically significant (p > 0.05) in cases with a history of diabetes mellitus.

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

The pooled OR was calculated using the Mantel-Haenszel method, and which revealed a relatively moderate degree of asymmetry. Begg's regression test produced a p value of 0.171, indicating a low probability of publication bias.

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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.

Acknowledgements

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References


