Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis

Short title: Chronic Pancreatitis and Pancreatic Cancer Risk

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ABSTRACT

Background and aims:
Chronic pancreatitis is a putative risk factor for pancreatic cancer. The aim of this study was to examine the magnitude and temporality of this association.

Methods:
A systematic review and meta-analysis. We searched MEDLINE and EMBASE for observational studies investigating the association between chronic pancreatitis and pancreatic cancer. We computed overall effect estimates with associated 95% CI using a random-effects meta-analytic model. The effect estimates were stratified by length of follow-up from chronic pancreatitis diagnosis to pancreatic cancer (lag period). Robustness of the results was examined in sensitivity analyses.

Results:
We identified 13 eligible studies. Pooled effect estimates (EEs) for pancreatic cancer in patients with chronic pancreatitis were 16.16 (95% CI: 12.59-20.73) for patients diagnosed with pancreatic cancer within two years from their chronic pancreatitis diagnosis. The risk of pancreatic cancer in patients with chronic pancreatitis decreased when the lag period was increased to 5 years (EE: 7.90; 95% CI: 4.26-14.66) or a minimum of 9 years (EE: 3.53; 95% CI: 1.69-7.38).

Conclusions:
Chronic pancreatitis increases the risk of pancreatic cancer, but the association diminishes with long-term follow-up. Five years after diagnosis, chronic pancreatitis patients have a nearly eight-fold increased risk of pancreatic cancer. We suggest that common practice on inducing a two-year lag period in these studies may not be sufficient. We recommend a close
follow-up in the first years following a diagnosis of chronic pancreatitis to avoid overlooking a pancreatic cancer.
INTRODUCTION

Cancer of the pancreas is a major cause of cancer-related death in western countries\(^1\). It has a dismal prognosis mainly due to nonspecific symptoms at a time when curative intervention may be possible and a very aggressive tumor biology\(^2\). The five-year survival rate has remained unchanged at approximately 5% throughout the past few decades\(^1,3\). To prevent the occurrence of pancreatic cancer, more knowledge on preventable risk factors is needed.

Despite extensive research, there are only few recognized risk factors for pancreatic cancer such as exposure to tobacco smoking, heavy alcohol intake, and diabetes mellitus\(^4\). Chronic pancreatitis may also increase the risk of pancreatic cancer\(^5\). However, previous research is limited by potential misclassification and possible confounding by tobacco smoking and alcohol consumption. Previously, this association was examined in two meta-analyses, both reporting a substantially increased risk\(^6,7\). However, these meta-analyses included only a subset of the published work available at the time, and they lacked information on the temporality of the association between chronic pancreatitis and pancreatic cancer.

We therefore conducted a systematic review and meta-analysis of all observational studies to examine the association between chronic pancreatitis and pancreatic cancer with special emphasis on exploring the temporality of this association.

METHODS

Search strategy and inclusion criteria

We conducted a search for all eligible studies in MEDLINE and EMBASE on November 28, 2016. In MEDLINE, we used the following search strings: ("Pancreatitis, Chronic"[Mesh] OR "Pancreatitis"[Mesh] OR "Pancreatitis, Alcoholic"[Mesh]) AND ("Pancreatic Neoplasms"[Mesh] OR "Neoplasms"[Mesh]) AND "Chronic pancreatitis AND pancreatic
cancer”. In EMBASE, we searched for “pancreas cancer'\text{exp} \text{AND} (chronic pancreatitis'\text{exp} \text{OR} \text{alcoholic pancreatitis'\text{exp} \text{OR} pancreas calcification'\text{exp})}\text{AND} \text{chronic pancreatitis' \text{AND} pancreas cancer'”. No filters regarding study type, language, or time period was applied to the search. The literature search and reference screening was conducted by one medical doctor (JK). If the title was too ambiguous to allow exclusion, we reviewed the abstract and decided whether or not to include the study. Reference screening and study selection was performed using Covidence (Teamsquare, Melbourne, Australia).

We included all observational studies that 1) examined an association between chronic pancreatitis and subsequent pancreatic ductal adenocarcinoma (pancreatic cancer), and 2) provided a relevant risk estimate in terms of odds ratio (OR), rate ratio (RR), standardized incidence ratio (SIR), or hazard ratio (HR). We subsequently excluded papers that did not present full-texts in English, Danish, Swedish or Norwegian and papers confined to patients with hereditary or tropical pancreatitis. Conference abstracts were ineligible for inclusion.

**Data extraction**

Data extraction was performed independently by two authors (JK and FVM). For each study, we extracted descriptive information (author, year, journal, setting, recruitment methods and period, study design, sample size, and method of verification of pancreatitis and pancreatic cancer), risk estimates with 95% confidence interval (CI), and information on variables used for matching or adjustment. One study lacked the desired risk estimate, which was obtained after contact with the lead author. Disagreements were settled by consensus.

**Assessment of study quality and risk of bias**

As there is no internationally agreed and properly validated quality score scale for use in reviews and meta-analyses, we used the “strengthening the reporting of observational studies in epidemiology” (STROBE) guidelines as a template for assessment of each study. We
identified key elements that could potentially introduce bias in the studies, including selection bias, information bias, and the possibility of unmeasured confounding.

**Statistical analyses**

Using the random-effects model of DerSimonian and Laird, we pooled the study specific risk estimates and calculated an overall effect estimate (EE) with associated 95% confidence interval (CI). Overall effect estimates are presented as forest plots. Risk estimates in terms of OR, RR, HR, and SIR were considered equivalent. We examined statistical heterogeneity using the I² statistic. To examine the temporality of the association between chronic pancreatitis and pancreatic cancer, we stratified the analyses by the time from pancreatitis diagnosis to pancreatic cancer diagnosis (i.e., the lag period). Most studies induced either none, one-year, or two-year lag periods, and four studies provided estimates with five-year lag periods. Only one study provided an estimate after ten years of follow-up, whereas another study presented an estimate following a nine-year lag period. We therefore grouped these two studies together as a minimum nine-year lag period, providing a proxy for the long-term relationship. Sensitivity analyses were performed to examine the robustness of our results. We restricted to studies with more than 50 cancers or exposed subjects as a proxy for studies with high statistical precision, studies without self-reported or unverified exposure or outcome, and studies with adjustment for tobacco exposure or alcohol consumption. Risk of publication bias was assessed using funnel plots and Egger’s test. Statistical analyses were performed using Stata 13.1 (Stata Corp LP, College Station, Texas, US).

**RESULTS**

**Literature search**
In EMBASE and MEDLINE, we identified 20,108 studies, of which 6,843 were duplicates and 13,110 were excluded based on the title. We screened the remaining 155 studies, excluding 148 papers for various reasons (Figure 1). We identified an additional six eligible studies through the reference lists of the reviewed papers. Thus, we included a total of 13 studies in this systematic review and meta-analysis.

Study characteristics and quality assessment

Among the 13 studies, four were case-control studies\textsuperscript{8,10-12} and nine were cohort studies\textsuperscript{5,13-20}. Study characteristics are given in Tables 1 and 2.

The cohort studies included between 170 and 11,972 individuals. Six of the nine cohort studies observed fewer than 50 cases of pancreatic cancer. In the case-control studies, the number of cases ranged from 210 to 2,639, and no study included more than 100 pancreatic cancer patients with a history of chronic pancreatitis. In general, pancreatitis and pancreatic cancer diagnoses were verified by clinical evaluation, the use of International Classification of Diseases [ICD] codes, or histology. One study lacked verification of the cancer diagnosis\textsuperscript{17}. In two case-control studies, diagnosis of pancreatitis was self-reported, leading to a risk of recall bias\textsuperscript{8,11}. In all but one cohort study\textsuperscript{5}, which included a matched comparison cohort, standardization was used for adjustment. All cohort studies standardized by age, six studies standardized by sex\textsuperscript{13-16,18,20}, three studies by calendar year of diagnosis\textsuperscript{13,14,17}, one study by district of residence\textsuperscript{13}, and one multicenter study by institution\textsuperscript{15}. In all case-control studies, the controls were matched to the cases by age and sex, or multivariate analyses were adjusted for these covariates. Two of the 13 studies adjusted for tobacco smoking in their analyses\textsuperscript{8,11}. General limitations of the included studies consist of no or only a one-year lag period from pancreatitis diagnosis to cancer, high risk of confounding by other risk factors such as smoking and alcohol, and risk of misclassification.
of both exposure and outcome due to possible treatment outside the study setting. A more detailed list of the main risks of bias in each study is given in Supplementary Table 1.

**Meta-analysis**

*Short-term risk*

The pooled effect estimate for pancreatic cancer among patients with chronic pancreatitis without any lag period between the two diagnoses was 7.96 (95% CI: 2.36-26.86). When restricting to studies with estimates for one- or two-year lag periods, our effect estimates were 6.09 (95% CI: 3.79-9.79) and 16.16 (95% CI: 12.59-20.73) respectively.

*Long-term risk*

The effect estimate of pancreatic cancer among patients with chronic pancreatitis who were followed for five years from pancreatitis diagnosis was 7.90 (95% CI: 4.26-14.66). The risk decreased when increasing the follow-up period to at least nine years (EE: 3.53; 95% CI: 1.69-7.38). The forest plot is depicted in figure 2.

**Sensitivity analyses**

In the first sensitivity analysis, we omitted studies with less than 50 cancers (cohort studies) or 50 exposed cases (case-control studies) and one year of follow-up, yielding an effect estimate of 6.09 (95% CI: 3.79-9.79). Further, when increasing this follow-up period to five years, the estimate decreased to 4.73 (95% CI: 3.44-6.50). When excluding studies with self-reported pancreatitis, unverified pancreatic cancers, and less than a two-year lag period between pancreatitis and cancer, the was 11.77 (95% CI: 6.88-20.12). In a fourth sensitivity analysis, we removed all studies with surgically treated chronic pancreatitis patients and less than two years of follow-up, which decreased the risk estimate (EE: 7.32; 95% CI: 3.18-16.83). When restricting to studies incorporating tobacco smoking in the multivariate model,
the risk was decreased (EE: 2.94; 95% CI: 0.73-11.83). All effect estimates from the sensitivity analyses are presented as forest plots in the Supplementary Figure 2-4.

**Publication bias**

The risk of publication bias was assessed using a funnel plot, which did not give rise to concerns about publication bias. Using the Egger test, we discovered no evidence of publication bias in any of the lag period groups.

**DISCUSSION**

In the present systematic review and meta-analysis, we found that patients with chronic pancreatitis are at an increased risk of pancreatic cancer compared with patients not affected by chronic pancreatitis. When excluding cancers occurring in the first two years following a diagnosis of chronic pancreatitis, the risk of pancreatic cancer was elevated 16-fold. Although this risk declines over time, it persists even after long-term follow-up. The risk was still eight-fold increased when introducing a five-year lag period from pancreatitis diagnosis to pancreatic cancer diagnosis. Our findings also suggest that patients with at least nine years of follow-up from their pancreatitis diagnosis still had over three-fold increased risk of pancreatic cancer compared with patients without chronic pancreatitis.

Our observed short-term association between chronic pancreatitis and pancreatic cancer risk is most likely due to initial misclassification of a pancreatic cancer as chronic pancreatitis. The risk of such misclassification is high due to similarities in clinical, radiological, and biochemical nature of these diseases resulting in a complex diagnostic process²¹.

The long-term risk observed in the present study can have several explanations. First, detection bias may be present, as patients with chronic pancreatitis are frequently admitted to
the hospital due to complications and comorbidity. Second, results are likely to be confounded by tobacco exposure and alcohol consumption. Both are well-established risk factors for pancreatic cancer and known to be more prevalent among chronic pancreatitis patients than the general population. Third, a causal relationship may exist between chronic pancreatitis and pancreatic cancer. As inflammation accumulates in the pancreas, pancreatic stellate cell activation may lead to carcinogenesis in genetically predisposed individuals. In fact, around 90% of all pancreatic cancers harbor mutations in the K-ras oncogene. In addition, K-ras mutations have been found in patients with chronic pancreatitis, indicating a common disease pathway. Despite this, only around 5% of patients with chronic pancreatitis develop pancreatic cancer, and some chronic pancreatitis patients with K-ras mutations never develop pancreatic cancer. The link between inflammation and cancer observed in this study corresponds to evidence from other organs, in which inflammation is known to increase the risk of cancer, for example in the colon.

When inferring causality, time is an essential factor. Pancreatic cancer cases occurring less than two years after chronic pancreatitis diagnosis is unlikely to be caused by pancreatitis. Thus, in epidemiological studies of pancreatitis and pancreatic cancer, it is common practice to exclude patients diagnosed with pancreatic cancer within one or two years following a chronic pancreatitis. Of the included studies in this meta-analysis, only four studies provided risk estimates when excluding patients with less than five years of follow-up. The steep decrease in pancreatic cancer risk when comparing our two- and five-year effect estimates supports our hypothesis that pancreatic cancer may be initially misclassified as chronic pancreatitis. The risk decrease also shows that a two-year lag period may not be sufficient to evaluate if a causal relationship exists in such studies. However, it should also be kept in mind that a lag-period from chronic pancreatitis symptoms to diagnosis can often last for many years. We recommend that future epidemiological studies on this topic
should incorporate a longer lag-period, e.g. five years, from chronic pancreatitis to pancreatic cancer diagnosis to sufficiently avoid the risk of initial misclassification.

To examine the effect of alcohol and tobacco smoking, we performed a sensitivity analysis, restricting to studies that adjusted for these risk factors. The association of chronic pancreatitis and pancreatic cancer risk was still three-fold increased, but the estimate had low precision. Four studies provided risk estimates for non-smokers similar to those for smokers or stated that smoking did not have any impact on the estimate\textsuperscript{15,18-20}, whereas one study found an increased risk of pancreatic cancer among smokers\textsuperscript{19}. Results were also disparate with regards to the effect of alcohol consumption, as one study found an increased risk among alcoholics\textsuperscript{14}, which contrasts with findings in another study\textsuperscript{10}. Given the heterogeneity between studies, it is difficult to evaluate the impact of smoking and alcohol on the risk estimates. Based on the existing literature and knowledge of risk factors for pancreatic cancer, it is plausible that some proportion of the excess pancreatic cancer risk seen among patients with chronic pancreatitis may be due to residual confounding by alcohol and tobacco smoking.

We note considerable heterogeneity among the 13 studies included in this systematic review and meta-analysis. Also, some studies included only few cancers or few patients exposed to chronic pancreatitis, leading to inflated risk estimates with low precision. This is also highlighted in our sensitivity analyses. When restricting the analyses to studies with more than 50 cancers or exposed subjects, effect estimates were more conservative and had higher precision. In three studies more than one-third of the patients were lost to follow-up\textsuperscript{8,11,16}, and in one study, only 55\% were males\textsuperscript{17}, increasing the risk of selection bias. Although three studies included few patients with hereditary pancreatitis, no cancers were seen among these patients\textsuperscript{16,19,20}, and this is therefore unlikely to explain our findings. When interpreting results from our sensitivity analyses, it is important to keep in mind that the numbers included are small. Thus, conclusions drawn from these analyses should be cautious.
Two meta-analyses have previously examined the association between chronic pancreatitis and pancreatic cancer, although both failed to include all available studies at that time. Raimondi et al.\textsuperscript{6}, analyzed seven studies using a narrow search strategy (including only MeSH terms “Pancreatitis” and “Pancreatic Neoplasms” and searching only MEDLINE). They provided risk estimates of 11.8 (95% CI: 5.8-24.1) and 5.8 (95% CI: 2.1-15.9) for one and two-year lag periods respectively. However, they did not state which studies were included in these two models, limiting reproducibility and comparison. Further, they did not include a discussion in their paper. In a meta-analysis of six studies, Tong et al.\textsuperscript{7} found an overall risk estimate of 10.35 (95% CI: 9.13-11.75). However, they included a study with unspecified pancreatitis and a study on a diabetic population, resulting in a very heterogeneous population, which limits generalizability. Tong et al. also examined the temporality of the association with risk estimates of 2.82 (95% CI: 2.12-3.76) and 2.25 (95% CI: 1.59-3.19) for at least five and 10 years of follow-up respectively, which are lower than our estimates. However, they included patients with both acute, chronic, and unspecified pancreatitis in their analyses. Such potential misclassification between acute and chronic may have underestimated the association, as acute pancreatitis is less likely than chronic pancreatitis to lead to pancreatic cancer\textsuperscript{28}. Misclassification of exposure is a general concern, as chronic pancreatitis can be very difficult to diagnose. In the present meta-analysis, most studies reported that chronic pancreatitis exposure was ascertained based on clinical evaluation and diagnostic criteria. Two studies included self-reported pancreatitis\textsuperscript{8,11}, four studies identified patients based on ICD codes with no information on the diagnostic process \textsuperscript{5,10,13,14}, and one study included patients from 1946\textsuperscript{15}, when diagnostic modalities were sparse, increasing the risk of misclassification.

Our study demonstrates that patients are at a substantially increased risk of pancreatic cancer following a diagnosis of chronic pancreatitis, especially in the first few years after diagnosis. Our findings may reflect those of Munigala et al.\textsuperscript{29} who suggested that
approximately 5% of all pancreatic cancer patients were initially misdiagnosed as chronic pancreatitis, and a potential diagnostic delay of up to two years. As this delay compromises the chance of curative intent treatment, the clinical consequences of misdiagnosing pancreatic cancer as chronic pancreatitis are very high. Therefore, clinicians should seek to conduct thorough examinations of patients with symptoms of chronic pancreatitis, and special awareness should be taken not to overlook a pancreatic cancer.

Although this misdiagnosis will likely decrease during the later years due to the increasing use of advanced diagnostic tools, the differential diagnostics between chronic pancreatitis and pancreatic cancer will likely represent a major clinical challenge for the coming years and should be subject for intensive investigation.

In conclusion, we found that patients with chronic pancreatitis have a markedly increased risk of pancreatic cancer. This risk declines over time, but it remains elevated almost ten years after a diagnosis of chronic pancreatitis. Some of the excess risk may be due to exposure to tobacco smoking and alcohol consumption, detection bias, and initial misclassification of cancer as pancreatitis. We suggest that the common practice to introduce a two-year lag between chronic pancreatitis and pancreatic cancer diagnosis may not be sufficient to avoid misclassification, and we recommend a close follow-up of patients following a chronic pancreatitis diagnosis.

**FIGURE LEGENDS**

Figure 1: Flowchart of the literature search.

Figure 2: Forest plots of 13 observational studies examining the association between chronic pancreatitis and pancreatic cancer risk, stratified by time from pancreatitis diagnosis to cancer.
REFERENCES


AUTHOR CONTRIBUTIONS

Study idea and design: JK, DCF; Acquisition, analysis, or interpretation of the data: JK, FVM, DCF; Initial drafts: JK, FVM; Critical revision for important intellectual content: JK, FVM, DCF. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

JK is accepting full responsibility for the conduct of the study and had access to the data and have control of the decision to publish.

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POTENTIAL COMPETING INTERESTS

None.