

Factors Related to Development of Pancreatic Adenocarcinoma in Patients With Chronic Pancreatitis on Long-term Follow-up: A Database Study

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ABSTRACT

Background: Chronic pancreatitis (CP) is a risk factor for pancreatic adenocarcinoma (PA). However, little is known about factors related to development of PA in CP.

Objective: To evaluate factors associated with PA in CP.

Methods: A national insurance database of 120 million US patients was used. Adults with an International Classification of Diseases, Ninth Revision (ICD-9) code for CP (577.1) from January 1, 2009, to December 31, 2014, were identified. Patients' age, sex, and ICD-9 codes for PA, bile duct obstruction, alcohol use, diabetes mellitus before and after diagnosis of CP, obesity, tobacco use, and type of insurance were obtained. Patients with CP without a unique identification number, missing dates for insurance coverage period, and with duration to end of follow-up or development of PA less than 2 years were excluded. The Cox proportional hazards regression model was used for analysis.

Results: The final analysis had 30,555 patients with CP including 219 patients (0.72%) with PA. The Cox proportional hazards regression model showed that in patients with CP age (hazard ratio [HR] = 1.07; 95% Confidence Interval [CI] = 1.03-1.1), male sex (HR = 2.1; 95% CI = 1.25-3.54), tobacco use (HR = 1.88; 95% CI = 1.1-3.23), and having commercial insurance (HR = 4.26; 95% CI = 1.63-11.11) were associated with a subsequent medical claim for PA. Duration of bile duct obstruction (HR = 0.999; 95% CI = 0.998-0.999) and presence of diabetes mellitus before CP (HR = 0.35; 95% CI = 0.19-0.63) were inversely related to subsequent diagnosis of PA.

Conclusion: PA was diagnosed in 0.72% of the patients with CP at least 2 years after the diagnosis of CP. Increasing age, male sex, tobacco use, having commercial insurance, absence of diabetes mellitus before CP, and shorter duration of bile duct obstruction were associated with a diagnosis of PA in patients with CP.

INTRODUCTION

Chronic pancreatitis (CP) is characterized by inflammation and fibrosis of the pancreas associated with loss of acinar and islet cells.¹ The prevalence of CP in the US has been estimated to be 41.76 per 100,000 population.² CP is a known risk factor for pancreatic adenocarcinoma (PA) and the relative risk (RR) of PA in patients with CP is estimated to be 13.3 (95% Confidence Interval [CI] = 6.1-28.9) and 16.16 (95% CI = 12.59-20.73) in 2 separate meta-analyses.^{3,4} However, incidence of PA in patients with CP in the US has not been reported in the literature. Similarly, the risk factors for PA are well known, but risk factors associated with development of PA in patients with

CP are not well described in the literature. This study used an insurance claims database to evaluate the 1) incidence of PA in adult patients with CP and 2) factors associated with the development of PA in adults with CP.

MATERIALS AND METHODS

Data Source

Data for this study were obtained from the Truven Marketscan Commercial Claims and Encounters database and the Truven Marketscan Medicare Claims and Encounters database. Truven Marketscan (www.truvenhealth.com) offers fully integrated pharmaceutical and medical claims data with relevant health plan enrollment and demographic information of patients with commercial or Medicare insurance. These data are nationally representative of the US population and include all practitioner, facility, and pharmaceutical claims for eligible beneficiaries. Truven collects data from a wide variety of insurance providers as well as large self-insured employers and includes data on approximately 20 million unique individuals each year. Enterprise Data Trust of the Center for Clinical and Translational Science at the University of Kentucky maintained this data set (www.ccts.uky.edu/ccts/truven-health-marketscan). The maintenance of this data set was supported by the National Institutes of Health National Center for Advancing Translational Sciences. The data relevant to this study were extracted in consultation with Enterprise Data Trust.

The database maintained by the University of Kentucky contained deidentified information regarding all health care-related claims made for 120 million patients based on International Classification of Diseases, Ninth Revision (ICD-9) billing and coding system from January 1, 2009, to December 31, 2014. The database also had information on start and end dates of insurance coverage and medication prescriptions for all these individuals during the same period. Each patient had a unique patient identification number that was not linked to any identifiable patient information, including medical record number, Social Security number, date of birth, or medical insurance. This database has been validated and used in previous publications.⁵⁻⁷

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Inclusion Criteria and Data Extraction

All the patients with an ICD-9 code for CP (577.1) between January 1, 2009, and December 31, 2014, along with the date of initial claim were identified in the data set. Demographics (age at the time of CP diagnosis and sex), type of insurance (commercial vs Medicare), and ICD-9 codes for PA (157.0-157.3), if present, were obtained for each patient. ICD-9 codes for the presence of other risk factors of PA, including obesity (278.00), tobacco use (305.1), alcohol use (303.9, 305), and diabetes mellitus (DM; 250.00), were obtained for each patient. We previously reported an association between bile duct obstruction and PA (odds ratio [OR], 7.72) in patients with CP.⁸ Therefore, the ICD-9 code for bile duct obstruction (576.2), when present, was obtained to further examine this association. Statins have been reported to decrease the risk of PA in the general population.⁹⁻¹¹ To explore the association between statin use and PA in patients with CP, details about statin use (start and end dates of any statin prescription) were also obtained for each patient. Lastly, we wanted to explore any association between liver cirrhosis and PA in patients with CP. Therefore, ICD-9 codes for hepatic cirrhosis (571.2, 571.5, 571.6) were obtained. The date of the first medical claim made for each diagnosis was also obtained for each patient.

Exclusion Criteria

Patients younger than age 18 years at the time of initial CP claim, patients with unknown sex, and patients with missing dates of initial claim for any of the diagnoses, or patients with missing dates for start or end of the insurance coverage were excluded. Patients with CP but without PA who had less than 730 days of follow-up after the initial diagnosis of CP was made were excluded, which ensured a minimum period of follow-up after the diagnosis of CP. Similarly, patients with CP and PA for whom the medical claim for CP was made less than 730

days before the medical claim for PA were excluded (Figure 1) to ensure that patients who may not actually have CP but have pancreatic parenchymal changes induced by PA that can mimic CP were excluded.

Data Processing

During the initial data screening, 65,571 duplicate entries were removed from the data set using the unique patient identification number. In patients with CP and PA, the presence of various exposures was adjusted on the basis of the timing of diagnosis of PA to reduce bias from overestimation. Therefore, bile duct obstruction, obesity, cirrhosis, and tobacco use in patients with PA were treated as not present if their initial medical claim was made after the medical claim for PA. Because CP itself can lead to DM, DM was categorized into DM diagnosis before CP, DM diagnosis after CP, and no DM. Statin use was treated as a binary variable as never use vs ever use. For patients with CP and PA, ever use of statin was considered as present if the statin prescription was given 90 days or more before the medical claim for PA.⁹⁻¹¹ For patients with CP but without PA, ever use of statin was considered as present if the statin prescription was for 90 days or more after a medical claim for CP was made.

Statistical Analysis

Descriptive statistics were used to perform exploratory analyses. Categorical data were described as proportions and analyzed using the χ^2 test. Continuous data were described as mean (standard deviation [SD]) or median (range) and analyzed using the *t*-test or Wilcoxon rank sum test, depending on the distribution of the variable. Time-to-event analysis was performed using the Cox proportional hazards regression model to analyze the effect of demographics and other variables in patients with CP on time to PA. Observations for time in patients with CP who did not have a medical claim for PA were censored on December 31,

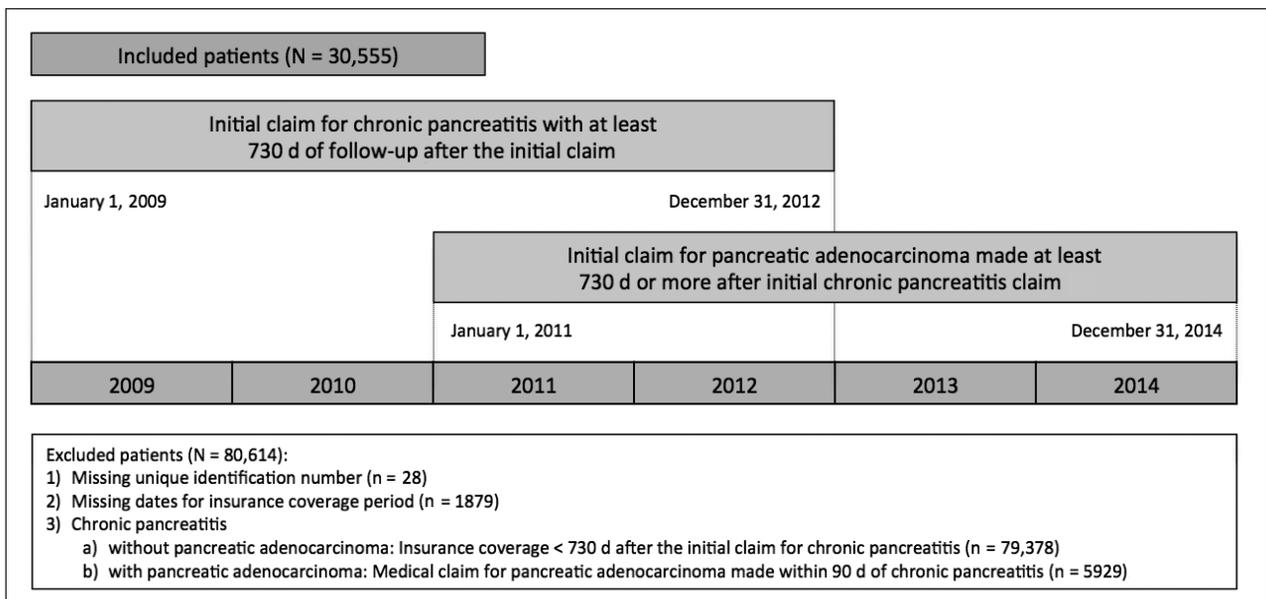


Figure 1. Study timeline and inclusion and exclusion criteria.

2014. Functional form of continuous variables and proportional hazards assumption for all the variables in the Cox proportional hazards regression model were checked using cumulative Martingale Residuals and Supremum test, respectively. One variable, duration of bile duct obstruction, violated the functional form assumption. This was corrected by obtaining the square of square of log transformation of the variable. A 2-sided $p < 0.05$ was considered significant. The analysis was performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Characteristics of patients with chronic pancreatitis with and without pancreatic adenocarcinoma

Characteristic	CP without cancer (n = 30,336)	CP with cancer (n = 219)	p value
Mean (SD) age, y	55.1 (15.12)	59.6 (13.38)	<0.001
Median (IQR) duration of CBD obstruction, d	1116.5 (690)	422 (919)	<0.001
Sex, No. (%)			
Men	14,519 (47.86)	131 (59.82)	<0.001
Women	15,817 (52.14)	88 (40.18)	
Diabetes, No. (%)			
Before CP	9884 (32.58)	76 (34.70)	0.22
After CP	3474 (11.46)	17 (7.76)	
Insurance status, No. (%)			
Commercial	22,732 (74.93)	140 (63.93)	<0.001
Medicare	7604 (25.07)	79 (36.07)	
Other characteristics			
Obesity, No. (%)	6772 (22.32)	26 (11.87)	<0.001
Tobacco (%)	7916 (26.09)	75 (34.25)	0.006
Alcohol, No. (%)	3279 (10.81)	30 (13.7)	0.17
Statin use	3066 (10.11)	21 (9.59)	0.80
Cirrhosis	8251 (27.2)	70 (31.96)	0.11

CBD = common bile duct; CP = chronic pancreatitis; IQR = interquartile range; SD = standard deviation.

Table 2. Cox proportional hazards regression model of demographics and other variables in patient with chronic pancreatitis patients with and without subsequent pancreatic adenocarcinoma

Variable	HR (95% CI)	p value
Age	1.07 (1.03-1.1)	0.001
Duration of bile duct obstruction ^a	0.999 (0.998-0.999)	<0.001
Male sex	2.1 (1.25-3.54)	0.005
Diabetes before chronic pancreatitis vs no diabetes	0.35 (0.19-0.63)	<0.001
Tobacco use	1.88 (1.1-3.23)	0.02
Commercial insurance	4.26 (1.63-11.11)	0.003
Alcohol	1.17 (0.57-2.42)	0.67
Obesity	1.55 (0.73-3.29)	0.26
Statin	1.44 (0.51-4.03)	0.49
Cirrhosis	0.77 (0.45-1.33)	0.35

^a Corrected form derived by taking the square of square of log conversion of duration of bile duct obstruction in days. CI = confidence interval; HR = hazard ratio.

RESULTS

A total of 111,169 (92.6 per 100,000; 95% CI = 92.1-93.1 per 100,000) adult patients had a medical claim of CP in the database. Of these patients, 80,614 were excluded because of missing unique identification number (n = 28), missing dates for insurance coverage period (n = 1879), CP duration less than 730 days in patients without PA (n = 79,378), and medical claim for CP made less than 730 days before the medical claim for PA (n = 5929). Some of the excluded patients had more than 1 criterion for exclusion (Figure 1). A total of 111,227 (92.7 per 100,000; 95% CI = 92.2-93.2 per 100,000) adult patients had medical claims for PA in the database during the study period.

The final analysis included 30,555 patients with CP, and 219 (720 per 100,000 ; 95% CI = 630-820 per 100,000) patients had PA at least 730 days after the diagnosis of CP. Median duration of follow-up for the entire cohort was 1225 days (range, 730-2256 days). Median duration between the medical claim for CP and the subsequent claim for PA was 1076 days (range, 733-2256 days). Incidence of PA in patients with CP was 2.016 per 1000 person-years (95% CI = 2.015-2.017 per 1000 person-years).

Patients with CP with and without a medical claim for PA were compared with each other for differences in demographics and other variables (Table 1). There was a statistically significant difference in the mean age between the 2 groups. Patients with CP and PA were older (mean [SD] age, 59.6 [13.38] years) than patients with CP without PA (mean [SD] age, 55.1 [15.11] years; $p < 0.001$) at the time of first medical claim made for CP. A higher proportion of men with CP had a medical claim for PA (59.82% vs 47.86%; $p < 0.001$). Similarly, a higher proportion of patients with CP with a medical claim for PA had medical claims for tobacco use (34.25% vs 26.09%; $p < 0.006$) and bile duct obstruction (30.59% vs 10.07%; $p < 0.001$) compared with patients with CP without PA. Obesity was present less commonly in patients with CP and PA (11.87% vs 22.32%; $p < 0.001$). Patients with CP and PA more commonly had Medicare insurance (36.07% vs 25.07%; $p < 0.001$) and less commonly had commercial insurance (63.93% v. 74.93%; $p < 0.001$) than patients with CP without PA. The median duration of bile duct obstruction was significantly shorter in patients with CP and PA (422 days; Q1 42 days, Q3 961 days) compared with patients with CP without PA (1116.5 days; Q1 812 days, Q3 1502.5 days; $p < 0.001$). No difference was found in the proportion of patients with medical claims for alcohol use ($p = 0.17$), DM before or after CP ($p = 0.22$) or cirrhosis ($p = 0.11$), or ever use of statin ($p = 0.8$) between the 2 groups.

The Cox proportional hazards regression model showed that increasing age (hazard ratio [HR] = 1.07; 95% CI = 1.03-1.1) was independently associated with diagnosis of PA in patients with CP. Similarly, male sex (HR = 2.1; 95% CI = 1.25-3.54), tobacco use (HR = 1.88; 95% CI = 1.1-3.23), and having commercial insurance (HR = 4.26; 95% CI = 1.63-11.11) were independently associated with a subsequent medical claim for PA in patients with CP. The presence of DM before CP (HR = 0.35; 95% CI = 0.19-0.63; Table 2) was inversely related to a subsequent medical claim for PA. The presence of DM after

CP did not have any association with subsequent medical claim for PA. Increasing duration of bile duct obstruction was associated with a decreased chance of subsequent diagnosis of PA (HR = 0.999; 95% CI = 0.998-0.999). Other variables, including obesity ($p = 0.26$), alcohol ($p = 0.67$), statin use ($p = 0.49$), and cirrhosis ($p = 0.35$), in patients with CP did not have any association with a subsequent claim for PA in the final regression model (Table 2).

DISCUSSION

This is the first study to evaluate the incidence of PA in patients with CP in the US (720 per 100,000) on the basis of a national deidentified database of 120 million patients with commercial or Medicare insurance. Pancreatic cancer incidence in the general population of this data set during the same period was 92.7 per 100,000 indicating that incidence of PA in patients with CP was 7.8 times the PA incidence in the general population. This estimate is similar to previously reported literature.^{3,4} The data regarding incidence of PA in patients with CP are limited. A European observational study of 2015 patients with CP found that PA developed in 56 patients (2.8%) undergoing long-term follow-up.¹² This estimate is slightly higher than in our study, which can be a result of the difference in demographics, risk factor profile of the study populations, and length of follow-up after diagnosis of CP. The present study has a large and diverse population; therefore, the results could be generalized to populations with commercial or Medicare insurance in the US.

This is also the first study to evaluate factors associated with the diagnosis of PA in patients with preexisting CP for 730 days or longer. Some of the risk factors for PA were found to be similar between the general population and patients with CP. The incidence of PA increases with increasing age in the general population. According to the Statistics, Epidemiology and End Results program, the incidence of pancreatic cancer increased exponentially for every 5-year increase in age after the age of 45 years.¹³ Increasing age was found to be associated with PA in patients with CP in this study, with each year increase in age after the diagnosis of CP increasing the chance of subsequent PA by 7% (Table 2). Tobacco use is also a proven risk factor for PA in the general population (OR = 1.2; 95% CI = 1.0-1.13).¹⁴ In our study, tobacco use increased the chance of subsequent diagnosis of PA by 88% (Table 2).

The present study found a difference in the risk factors for PA between the general population and patients with CP. No difference in risk of PA has been found between men and women in general population, when adjusted for other risk factors.¹⁵ The present study found that men with CP were 2 times more likely to have a subsequent diagnosis of PA even after adjusting for other risk factors for PA. DM has been reported to be associated with an increased risk of PA in the general population in a meta-analysis of 35 cohort studies (RR = 1.94; 95% CI = 1.66-2.27).¹⁶ In the present study, patients with CP and DM before CP had 65% less chance of having subsequent PA compared with patients with CP without DM. The precise reason for this observation is not clear. However, it could

be hypothesized that patients with CP without preexisting DM may be more prone to developing malignant tumors at a cellular level because of differences in inflammatory and/or gene regulation-related factors. Increasing body mass index is an independent risk factor for PA in the general population (RR = 1.10; 95% CI = 1.07-1.14).^{17,18} However, obesity was not associated with PA in patients with CP in this study. Evidence regarding statins and risk for pancreatic cancer has been mixed. Some studies have found that statin use decreases the risk of PA in the general population (ORs = 0.33-0.66).^{9,10} However, recently, statin use was not found to reduce risk of PA.¹⁹ In the present study, statin use of at least 90 days was not associated with decreased risk of PA in patients with CP. Similarly, the data on PA risk with alcohol use has been equivocal. In one study, binge drinking (OR = 3.5) and heavy alcohol use (> 22 drinks per week for > 20 years; ORs = 3.1-4.2) were associated with increased risk of PA.²⁰ However, in other studies, alcohol use was not associated with increased risk of PA.²¹⁻²³ In the present study, alcohol use was not associated with increased chance of PA diagnosis in patients with CP. To date, no data are available on insurance status and risk of PA. Our study found that patients with CP with commercial insurance had a 3.9-fold chance of having subsequent PA compared with patients with CP on Medicare. Although insurance status by itself is not a risk factor for PA, this finding highlights the inherent difference in US patient populations even after adjustment for other risk factors for PA. This difference in populations may be ascribed to factors that could not be controlled for in this study (eg, race) or other unknown confounders. Further studies are needed to verify these findings and to evaluate the factors responsible for difference in PA risk in patients with CP with different insurances.

The present study found that increasing duration of bile duct obstruction (by a factor of square of square of log transformation of bile duct obstruction in days) in patients with CP is inversely related to a subsequent medical claim for PA (HR = 0.999). This association does not imply causality but rather the significance of carefully screening patients with CP with new-onset bile duct obstruction for PA. The results also imply that the longer patients with CP have bile duct obstruction, the less likely it is to be related to underlying PA.

The present study has several strengths. The patients with CP were selected from a very large patient sample (15 million), representing a diverse population in the US. The rate of development of PA in patients with CP is low, and a large sample size allowed this estimate to be reliable with a narrow CI (0.72%; 95% CI = 0.63%-0.82%). The study had robust exclusion criteria. Patients with missing data for any of the variables were excluded, and only patients with data available for all the variables were included in the study. Patients with CP without PA had a minimum of 2 years of follow-up to ensure an appropriate follow-up period and avoid underestimation of PA in patients with CP with short follow-up. On the other hand, patients with CP who developed PA had a minimum of 2 years between the 2 claims to ensure exclusion of patients who may not actually have CP but have pancreatic parenchymal changes induced by PA that can mimic CP.³

There are some limitations to this study. One of these limitations relates to the use of administrative codes to identify the exposures and outcomes. However, ICD-9 codes have been used in the literature to identify CP, with variable accuracy ranging from 51% to more than 85%.²⁴⁻²⁶ ICD-9 codes are highly sensitive for identifying PA (95%) and cirrhosis (82.6%-95.7%).^{27,28} ICD-9 codes for obesity have high specificity (> 90%) with a lower sensitivity (up to 30%).^{29,30} ICD-9 codes are valid indicators for identifying smokers.³¹ The claims diagnoses based on ICD-9 coding may underrepresent the true prevalence of certain conditions in the study population. However, underreported chronic conditions will only yield conservative estimates rather than overestimation of the association between different variables and PA in patients with CP. Moreover, obtaining data of such large magnitude as in this study is not possible by other methods. Truven MarketScan data does not provide information on patient race, mortality, underlying cause of CP, or family history of pancreatic cancer. Race, hereditary pancreatitis, and a family history of pancreatic cancer can affect the risk of PA independent of other factors noted in the study. However, this study provides an overall estimate of PA in patients with CP. Additional studies are needed to evaluate the effect of these factors on the risk of PA in patients with CP. The follow-up period for patients with CP was relatively short (median follow-up, 1225 days). However, use of time-to-event analysis using the Cox proportional hazards regression model had the advantage of adjusting the risk estimate for each patient on the basis of the period of follow-up. Lastly, the study population was composed of commercially insured or Medicare patients; therefore, the results of this study may be less applicable to Medicaid patients or veterans.

CONCLUSION

CP was present in 0.093% of the study population. A subsequent medical claim for PA was made in 0.72% of the patients with CP at least 2 years after the initial claim for CP. Increasing age, male sex, tobacco use, having commercial insurance, absence of DM, and shorter duration of bile duct obstruction were associated with a diagnosis of PA in patients with CP. Additional prospective cohort studies of patients with CP are needed to verify these findings. ❖

Disclosure Statement

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The author(s) have no conflicts of interest to disclose.

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