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Exploring prior diseases associated with pancreatic cancer

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ABSTRACT

Background Pancreatic cancer (PC) is among the most deadly forms of cancer; however, the risk factors of PC have yet to be sufficiently identified. In the present study, we sought to screen all prior diseases associated with PC incidence concurrently and construct pathways for the diseases. *Materials and methods* This total population-based case–control study used data collected from Taiwan's National Health Insurance Research Database for the period covering 1997–2013. The case group included 3726 patients newly diagnosed with PC, who were precisely matched to 3726 controls based on gender, age, residence, and insurance premiums. Stepwise multivariate logistic regression was used to screen previous diseases in windows of 1, 2 …, 9 years prior to the first diagnosis of PC. Path analysis was used to construct the pathways between relevant prior diseases and PC. *Results* Within 1 year prior to PC diagnosis, a total of 11 diseases were significantly correlated with PC, included 9 positive and 2 negative associations. Path analysis identified diabetes, pancreatitis as diseases with direct positive pathways to PC incidence, and dementia with direct negative pathways. *Conclusions* It appears that diabetes, peptic ulcer, and digestive conditions were the prior diseases associated with PC incidence.

ARTICLE INFO

Keywords: Pancreatic cancer; diabetes; population-based study; path analysis

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Introduction

Pancreatic cancer (PC) is currently the third most lethal form of cancer,[1] and is expected to become the second leading cause of cancer-related death by 2030.[2] Most patients with PC remain asymptomatic until the disease enters the advanced stage and invades or metastasizes to distant organs. As a result, disease mortality is very close to disease incidence.[3] Based on data from the surveillance and epidemiology of Taiwan in 2016, PC is the eighth leading cause of cancer death with an age-adjusted annual incidence of 6.7 cases per 100,000 persons. The mortality rate is 6.3 deaths per 100 000 person-years due to the poor prognosis for PC, and the 5-year survival rate is estimated at 8%.[4] It is therefore crucial that PC be identified as early as possible. There is a growing body of evidence suggesting that PC is influenced by multiple factors.[5] Individuals with specific inherited conditions or a familial history of PC face an elevated risk of contracting the disease.[6,7] Other factors such as new-onset diabetes, preexisting diabetes, advanced age, cigarette smoking, obesity, or a history of chronic pancreatitis also increase the risk to a lesser degree.[7-15] A number of epidemiological diseases, including peptic ulcer, have been linked to PC.[16-19] Our objective in the current study was to screen all prior diseases that may be linked to PC via rigorous database analysis in order to characterize the association between prior diseases and the incidence of PC.

Materials and methods

Ethics statement

Approval for this study was obtained from the Institutional Review Board of National Taiwan Normal University (Research ethics committee No.: 201710HM0101). Written consent was exempted because the data was obtained from the National Health Insurance Research Database (NHIRD) of Taiwan, which contains de-identified secondary data released for research purposes.

Data sources

This study used data files pertaining to outpatient care, inpatient care, ambulatory care, and details of prior medical conditions from the NHIRD in Taiwan for the years 1997–2013, and Registry for Catastrophic Illness Patient Database (RCIPD) in Taiwan for the same period. In 1995, the National Health Insurance (NHI) program in Taiwan, which is a single-payer insurance system operated by the government, was established to ensure the health of the entire nation and prevent social problems caused by poverty and disease. As of 2014, 99.9% of Taiwan's population was enrolled.[20] RCIPD is based on the list of catastrophic illness from the Ministry of Health and Welfare in Taiwan. The insurance system records all patients with 30 categories of catastrophic illness, including malignant neoplasm, uremia, and chronic psychotic disorders. The attending physician of any patient diagnosed with a catastrophic illness is also encouraged to submit relevant information to the RCIPD. A committee formally reviews the applications, and if approved, patients are then exempted from co-payment during the effective. Thus, the data used in this study can be regarded as comprehensive.[21]

Study design and population

In this population-based matched case-control study, PC cases were defined as RCIPD patients newly diagnosed with PC (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM: 157.xx) between 2010 and 2013. We excluded the following patients:

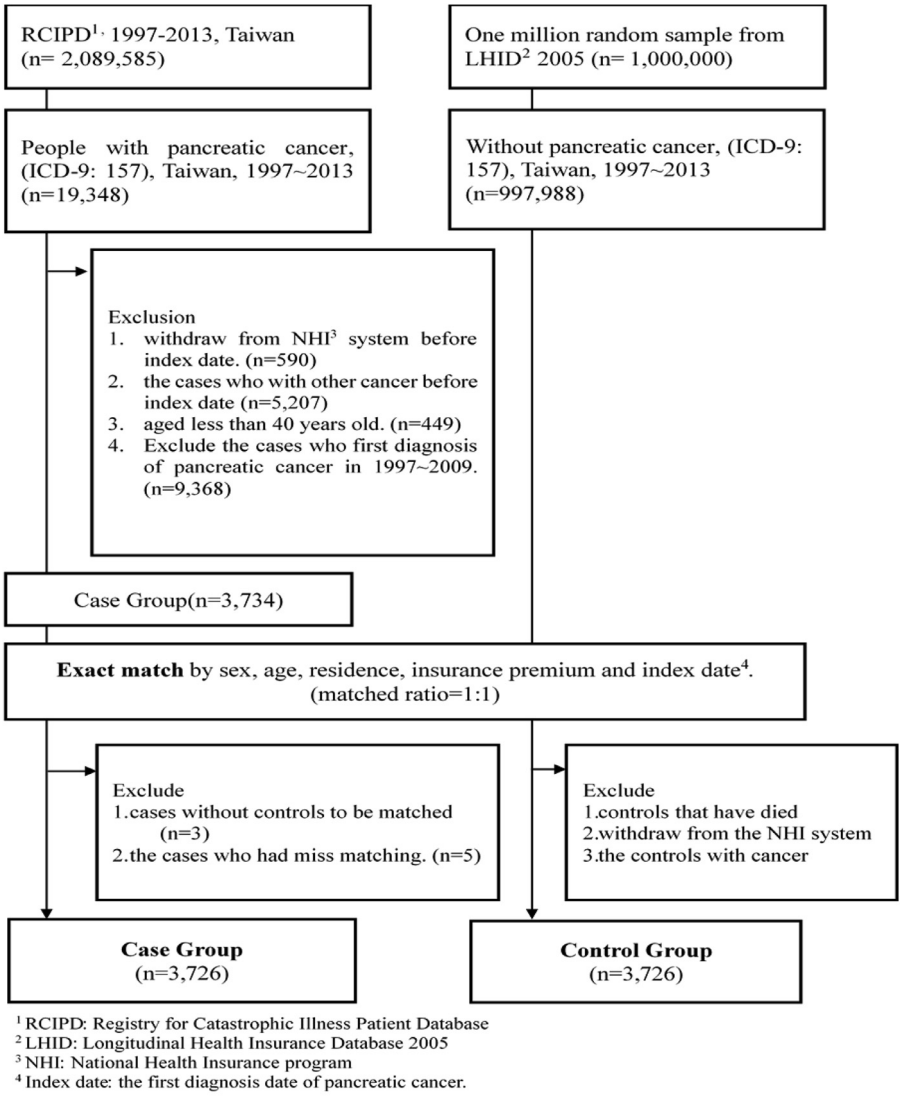

Fig. 1. Flowchart of subject selection process.

(1) those who withdrew from the NHI system prior to the index date or whose medical service data was incomplete, (2) those aged <40 years, (3) those diagnosed with cancer prior to the index date, (4) those with a first diagnosis of PC between 1997 and 2009. The index date was defined as the date on which the patient received an initial diagnosis of PC. This date was also used in assigning a matched control (Fig 1). The controls group employed the 2005 Longitudinal Health Insurance Database (one million random samplings longitudinal database, 1997-2013), also assigned to the respective matched controls, and this was who were NHI enrollees without a PC diagnosis (ICD-9 157) before the index date. The control group contained 3726 individuals matched to the PC patients based on gender, age, location of residence, and insurance premiums.

The definitions of the prior diseases were based on the first 3 digits of the codes listed in ICD-9-CM. Inclusion criteria required that each ICD-code existed for at least 1 year and incurred at least 2 outpatient visits or inpatient diagnosis. Prior diseases associated with PC were screened through windows of 1, 2, 3, ..., 9 years prior to the date of the first diagnosis of PC. We excluded the past 1, 1-2, 1-3,1-4,1-5,1-6,1-7, and 1-8 year of diseases prior to the first diagnosis date of PC. For example, screen -3 year prior diseases we excluded the past 1-2 years of diseases prior to the first diagnosis date of PC (as supplement figure 1). All medical claims between 1997 and 2013 containing this code were obtained from the NHIRD for further analysis. Finally, we constructed pathways related to the identified prior diseases in order to plot the relationships among the diseases.[22]

Statistical analysis

The Chi-square test was used to compare the distributions of demographic factors among patients newly diagnosed with PC and the controls (ie, gender, diagnosis age, location of residence, and insurance premiums). Stepwise multivariate logistic regression was used to identify the diseases associated with PC and derive the adjusted odds ratio (OR). The false discovery rate was used to adjust p-values in order to avoid an increase in type I errors under the effects of multiple testing. Two-sided data analysis was performed using the statistical package SAS 9.4 (SAS Institute Inc., Cary, NC, USA). *P-value* < 0.05 indicated significant.

Path analysis was applied to the relevant diseases for periods of 1-year prior index date to construct pathways from the identified diseases to PC. The chi-square test, standardized root mean square residual, root mean square error of approximation, comparative fit index, goodness-of-fit statistic, tucker Lewis index, and root mean square residual were used to evaluate the overall goodness-of-fit of the correction path analysis model.

We fitted a hypothesized pathway model to the PC, and then executed a correction model to establish positive and negative associations using modification indices (MI). The correction procedure modified the initial model one path at a time with the aim of improving the goodness-of-fit. Candidate paths where MI > 0 were then added to the correction model (as supplement figure 2). The final step involved systematically trimming nonsignificant pathways based on coefficient estimates with a *P*-value of > 0.05. In each step, interim evaluations of MI were conducted to identify relevant pathways that arose after simplifying the model. We included in the final correction model only the significant paths ($P < 0.05$) for which there was an acceptable overall goodness-of-fit. The overall process was stopped when no additional significant pathways were suggested by the MI. The direct and indirect effects of prior diseases on PC incidence were defined using the model constraint procedure and the maximum likelihood robust estimator. Total effects (determined as the sum of direct effects and indirect effects) were also calculated. Data analysis was performed using AMOS 21 (IBM Corp., 2012). Similar analysis was used in our previous research on diseases correlating with amyotrophic lateral sclerosis.[22]

Results

Sample characteristics

This study comprised 3726 patients newly diagnosed with PC (aged $\geq$40 years) and 3726 gender-, age-, residence-, and insurance-premium-matched controls. Descriptions and a comparison of characteristics are presented in Table 1. Among the PC patients, 55.72% were male and most were aged $>$65 years (Mean $\pm$ SD: 67.74 $\pm$ 12.16). Approximately 56.36% were urban residents, and 61.51% were insurance-premium-dependent, had a low income, or had insurance premiums of less than NT$20,000.

Table 1
Characteristics of patients with and without pancreatic cancer.

Characteristic	Pancreatic cancer, n = 3 726 (%)	Nonpancreatic cancer, n = 3726 (%)	*P*-value
Gender			
Female	1650 (44.28)	1650 (44.28)	>0.99
Male	2076 (55.72)	2076 (55.72)	
Pancreatic cancer diagnosis age (year)			
40-64	1592 (42.73)	1597 (42.86)	0.99
65-75	978 (26.25)	973 (26.11)	
≥75	1156 (31.03)	1156 (31.03)	
Residence			
Highly urbanized city	1050 (28.18)	1050 (28.18)	>0.99
Median urbanized city	1050 (28.18)	1050 (28.18)	
New town	630 (16.91)	630 (16.91)	
General town	566 (15.19)	566 (15.19)	
Agricultural town	430 (11.54)	430 (11.54)	
Insurance premium			
Fixed premium and dependent	1391 (37.33)	1391 (37.33)	>0.99
Less than NTD*20,000	901 (24.18)	901 (24.18)	
NTD 20,000 ~39,999	1167 (31.32)	1167 (31.32)	
NTD 40,000 or more	267 (7.17)	267 (7.17)	

* 1 US $=32.1 NTD in 2008, NTD=New Taiwan Dollar.

Prior diseases and incidence of pancreatic cancer

As shown in Table 2, 11 prior diseases were significantly associated with the incidence of PC (diseases that occurred within 1 year prior to the initial diagnosis of PC). This group included 9 positive and 2 negative associations: diabetes (code: 250, OR = 1.4), neoplasm of unspecified nature (code: 239, OR = 1.9), and diseases of digestive system including pancreatitis (code: 577, OR = 1.9), gastrointestinal hemorrhage (code: 578, OR = 1.4), functional digestive disorders (code: 564, OR = 1.2), and peptic ulcer (code: 533, OR = 1.2) were positive association PC incidence. Symptoms related to nutrition (code: 783, OR = 1.8), those involving the abdomen and pelvis (code: 789, OR = 1.3), and those involving the skin and other integumentary tissue (code: 782, OR = 1.2) were also significantly positive associated with PC. Dementia (code: 290, OR = 0.5) and diseases of pulp and periapical tissues (code: 522, OR = 0.8) were negatively associated with PC.

As shown in Table 3, we screened all prior diseases associated with PC using windows ranging in length from 1 to 9 years (in 1 year increments) prior to the index date. Diseases with an early positive effect on PC incidence (ie, from 8 years prior to first diagnosis) included diabetes (code: 250), peptic ulcer (code: 533), symptoms involving abdomen and pelvis (code: 789), symptoms involving skin and other integumentary tissue (code: 782), and functional digestive disorders (code: 564).

Effects of prior disease on incidence of pancreatic cancer

Goodness-of-fit statistics revealed that the final correction models were acceptable. (see Supplementary Table 1) Table 4 presented the prior diseases with total, direct, and indirect effects on PC incidence for a 1-year period prior to PC diagnosis. Total positive effects were identified in 6 of the prior diseases, including diabetes (code: 250), pancreatitis (code: 577), peptic ulcer (code: 533), symptoms involving the abdomen and pelvis (code: 789), functional digestive disorders (code: 564), and symptoms involving the skin and other integumentary tissue (code: 782). Dementia (code: 290) with a total negative effect. Diabetes (code: 250) and pancreatitis (code: 577) were shown related high total positive effect compare to other diseases in the model; that is, with a direct positive or negative pathway to PC incidence (Fig 2).

Table 2
Distribution of diseases in the 1 year prior to the initial diagnosis of PC.

IICD*	Diseases		Pancreatic cancer, n = 3726(%)	Non-pancreatic cancer, n = 3726 (%)	FDR†	OR‡
290	Dementia	Yes	90 (2.42)	142 (3.81)	0.001	0.5
		No	3636 (97.58)	3584 (96.19)		
522	Diseases of pulp and periapical tissues	Yes	1325 (35.56)	1455 (39.05)	0.002	0.8
		No	2401 (64.44)	2271 (60.95)		
533	Peptic ulcer	Yes	1162 (31.19)	916 (24.58)	<0.001	1.2
		No	2564 (68.81)	2810 (75.42)		
564	Functional digestive disorders	Yes	1624 (43.59)	1357 (36.42)	<0.001	1.2
		No	2102 (56.41)	2369 (63.58)		
782	Symptoms involving skin and other integumentary tissue	Yes	407 (10.92)	305 (8.19)	<0.001	1.2
		No	3319 (89.08)	3421 (91.81)		
789	Other symptoms involving abdomen and pelvis	Yes	1399 (37.55)	1069 (28.69)	<0.001	1.3
		No	2327 (62.45)	2657 (71.31)		
250	Diabetes mellitus	Yes	1209 (32.45)	918 (24.64)	<0.001	1.4
		No	2517 (67.55)	2808 (75.36)		
578	Gastrointestinal hemorrhage	Yes	187 (5.02)	118 (3.17)	<0.001	1.4
		No	3539 (94.98)	3608 (96.83)		
783	Symptoms concerning nutrition	Yes	69 (1.85)	34 (0.91)	0.001	1.8
		No	3657 (98.15)	3692 (99.09)		
239	Neoplasm of unspecified nature	Yes	92 (2.47)	49 (1.32)	<0.001	1.9
		No	3634 (97.53)	3677 (98.68)		
577	Pancreatitis	Yes	122 (3.27)	49 (1.32)	<0.001	1.9
		No	3604 (96.73)	3677 (98.68)		

* ICD: International Classification of Diseases, ninth revision.
† FDR: False discovery rate less than 0.05 were showed in this table.
‡ OR: Odds-ratio with significant false discovery rate (FDR) less than 0.05 were showed in this table.

Table 3
Prior disease associated with pancreatic cancer as determined using multivariate analysis with stepwise selection (2010-2013, n = 7452).

ICD*	Diseases name	OR†, year prior to date of first diagnosis								
		1	2	3	4	5	6	7	8	9
290	Dementia	0.5	0.5	0.5	0.5					
522	Diseases of pulp and periapical tissues	0.8	0.8	0.8						
533	Peptic ulcer	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.3
564	Functional digestive disorders	1.2	1.1	1.1	1.1	1.1				
782	Symptoms involving skin and other integumentary tissue	1.2	1.2	1.2	1.3	1.3	1.2			
789	Other symptoms involving abdomen and pelvis	1.3	1.3	1.3	1.3	1.2	1.2	1.2	1.1	
250	Diabetes mellitus	1.4	1.3	1.3	1.3	1.3	1.3	1.3	1.3	
578	Gastrointestinal hemorrhage	1.4	1.3							
783	Symptoms concerning nutrition	1.8	1.8							
239	Neoplasm of unspecified nature	1.9	2	1.8						
577	Pancreatitis	1.9	1.7	1.9						

* ICD: International Classification of Diseases, ninth revision.
† OR: Odds-ratio with significant false discovery rate (FDR) less than 0.05 were showed in this table.

Discussion

This was a rare nationwide study aimed at identifying the prior diseases for PC. We used stepwise multivariate logistic regression analysis and path analysis with windows of 1, 2, 3…9 years prior to the first diagnosis of PC. The following diseases presented an early (ie, 8 years

Table 4
Total, direct, and indirect effects of significant prior diseases on pancreatic cancer incidence in the 1 year period prior to the date of PC diagnosis

ICD	Diseases name	Direct effects*	Indirect effects*	Total effects*
533	Peptic ulcer	0.000000	0.007530	0.007530
789	Other symptoms involving abdomen and pelvis	0.000000	0.005943	0.005943
564	Functional digestive disorders	0.000000	0.002145	0.002145
782	Symptoms involving skin and other integumentary tissue	0.000000	0.003128	0.003128
250	Diabetes mellitus	0.047647	-0.000156	0.047492
577	Pancreatitis	0.051598	0.000000	0.051598
290	Dementia	-0.043284	0.000000	-0.043284
578	Gastrointestinal hemorrhage	0.000000	0.000000	0.000000
522	Diseases of pulp and periapical tissues	0.000000	0.000000	0.000000
783	Symptoms concerning nutrition	0.000000	0.000000	0.000000
239	Neoplasm of unspecified nature	0.000000	0.000000	0.000000

* Total effect reflects an association between prior diseases and pancreatic cancer incidence via all paths in the model; an indirect effect reflects this association minus the direct effect of any path from a prior disease to pancreatic cancer incidence; and a direct effect is simply the total effect minus the total indirect effect.

prior to the index date) positive association with PC incidence: diabetes (code: 250), peptic ulcer (code: 533), and symptoms involving the abdomen and pelvis (code: 789). Diabetes and pancreatitis were shown to have a direct positive effect on PC incidence, whereas dementia was shown to have a direct negative effect. A number of these prior diseases have been described in the literature in a manner similar to the present study.[7,9,16-18,23-28]. Endocrine system and gastrointestinal system diseases may have a beneficial effect on PC incidence.

Diabetes and pancreatitis can lead to PC.[25] Previous research has indicated that patients with long-term diabetes are susceptible to PC, and patients newly diagnosed with diabetes face an elevated risk of developing PC within 2 years.[26] A number of studies have posited that diabetes is a cause of PC, whereas other studies cited diabetes as a complication of PC. One review study pointed out that at least 30% of diabetes patients are affected by PC. That study also reported that diabetes and metabolic syndrome are risk factors for PC.[12] Epidemiological studies have also suggested that pancreatic ductal adenocarcinoma is a cause of diabetes. This has prompted oncologists to differentiate new-onset diabetes caused by pancreatic ductal adenocarcinoma, as this may allow for the early diagnosis of PC.[24, 29] Similarly, our findings indicate that diabetes may be an early sign of PC.

Our results indicate an association between PC and gastrointestinal diseases, such as peptic ulcer (code: 533), functional digestive disorders (code: 564) as well as symptoms involving the abdomen and pelvis (code: 789) and gastrointestinal hemorrhage (code: 578). In one study, the symptoms most commonly observed prior to diagnosis with PC included indigestion, loss of appetite, and fatigue. Note that none of these were reported more frequently in the cancer group than in the without cancer group.[30] Subsequent symptoms of jaundice, changes in stool or urine color, weight loss, fatigue, changes in bowel condition, loss of appetite were more common in patients with PC than in those without cancer. Previous indicated that the early symptoms of PC typically signify benign disease, and are often attributed to the coexisting disorders.[31] This makes it very difficult to obtain a conclusive diagnosis of PC in a short period of time.

We found that peptic ulcer (code: 533) had an early positive effect on PC incidence from 9 year prior to the diagnosis. In one prospective cohort study,[17] 274 PC events were observed during an 18-year follow-up period. Individuals with gastric ulcer faced a higher risk of contracting PC than were those without peptic ulcer (RR, 1.83; 95% confidence interval [CI]: 1.13-2.97), and the risk was still significantly higher at 10-19 years after diagnosis of gastric ulcer (RR, 2.89; 95% CI: 1.26-6.64). There is no doubt that Helicobacter pylori is a risk factor for peptic ulcer disease and gastric cancer and may indeed be etiologically related to PC. In one case-control study investigating the association between H. pylori-carrying and exocrine PC, subjects with H. pylori or Cag A + strains were shown to have a statistically significant elevated risk of contracting PC (OR = 1.87, 95%CI = 1.05-3.34; OR = 2.01, 95%CI = 1.09-3.70).[19] One registry-based retrospective

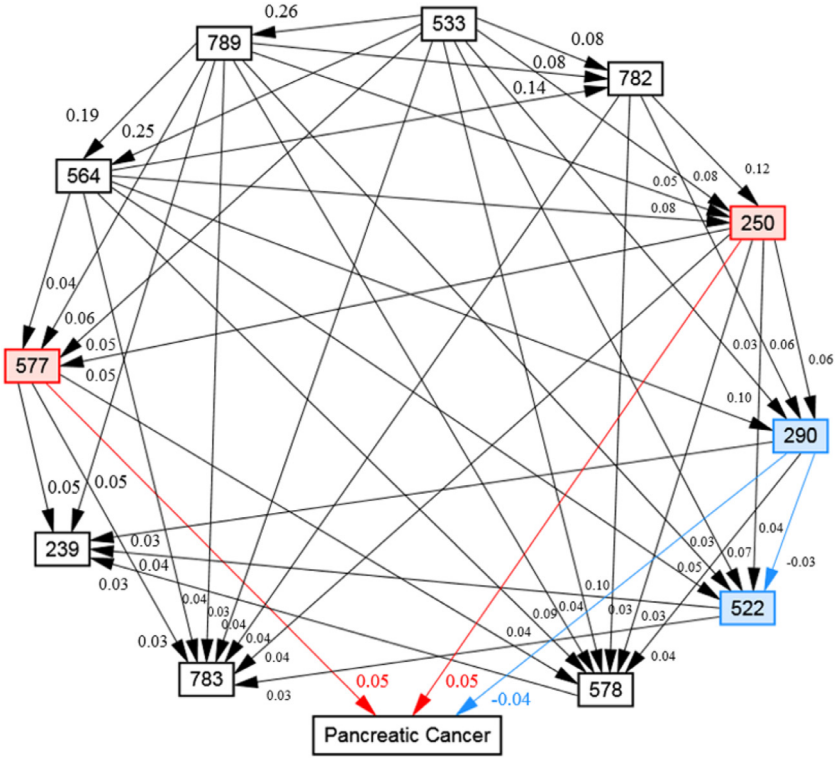

Fig. 2. Final path analysis model for diseases associated with pancreatic cancer prior to 1 years of first diagnosis. The red and blue lines indicate positive and negative direct links of prior diseases with pancreatic cancer, respectively. The International Classification of Diseases, Ninth Revision codes are displayed in the box. (Color version of figure is available online.)

cohort study reported that during a 3-38 year follow-up period, the risk of PC was 20% higher among patients with untreated gastric ulcer (95% CI=10%-40%).[18]

The most common causes of exocrine pancreatic diseases include acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Glandular damage caused by recurrent episodes of acute pancreatitis can lead to irreversible chronic pancreatitis. There is mounting evidence that chronic pancreatitis is an important risk factor for PC.[32] In a cohort study in China, Hao et al[9] found that the risk of contracting pancreatic cancer was significantly higher among patients with chronic pancreatitis than among the general population. It is also possible that acute pancreatitis is the first manifestation of pancreatic cancer. Rijkers et al[33] found that the incidence of pancreatic cancer among patients with chronic pancreatitis was nearly 9-fold higher than among patients with nonchronic (acute) pancreatitis. It has been reported that severe acute pancreatitis can lead to gastrointestinal bleeding, perforation of the pancreas, and infection (abdominal and general).[34]

Typical symptoms of pancreatitis include abdominal pain (code: 789) and functional digestive disorders (code: 564).[23] Pancreatic enzymes, bile salts, and intact intestinal mucosa are crucial to the process of fat digestion and absorption. Insufficient pancreatic exocrine enzymes due to pancreatitis can lead to excessive dyspepsia and the malabsorption of fat. As a result, many PC patients present symptoms associated with the digestive tract, such as constipation or diarrhea. Pancreatic duct rupture with repeated inflammation can lead to pseudo cysts, whereas erosion of the peripancreatic artery may lead to pseudo aneurysms and gastrointestinal bleeding. Scarring and fibrosis may cause duodenal or bile duct obstruction, the presentation of which is similar to the symptoms of jaundice (code: 782).[7]

A number of studies have noted that patients with dementia face a lower risk of developing cancer.[27] Nonetheless, many researchers believe that cognitive and behavioral difficulties prompt many Alzheimer's disease (AD) patients to disregard cancer-related symptoms. Another study posited that AD patients are less likely to develop cancer based on the fact that cancer is characterized by uncontrolled cell proliferation, whereas the neurodegenerative changes associated with AD are characterized by a premature progressive loss of neuronal cells.[28] A population-based longitudinal study in Korea reported a negative correlation between AD and cancer. That study specifically mentioned the risks associated with the pancreas and reported that the risk of PC was lower in the AD group than in the control group (hazard ratio, 0.55).[35]

The major strength of the current study lies in our use of a nationwide catastrophic illness database to validate PC diagnoses. We identified prior diseases associated with PC over various time periods prior to the date of PC diagnosis and constructed comprehensive pathways between those diseases and PC. Nonetheless, one substantial limitation of this study was the limited amount of information related to other potential confounders, such as body mass index, dietary patterns, blood pressure, blood sugar, smoking, family history, and therapy for diabetes. Disease onset and diagnosis may differ according to the economic status and residence of patients, due to the fact that those variables can affect access to physician. Nonetheless, the relationship between PC and diabetes, pancreatitis, peptic ulcer, and symptoms involving the abdomen and pelvis were in line with many previous studies in the literature. Moreover, our use of path analysis revealed relevant diseases (eg, dementia), which were seldom reported in previous studies.

Authors' contributions

Charles Tzu-Chi Lee (acquisition of data; developing the concept and design of the study; writing the first draft).

Jie-Xi Hu (developing the concept and design of the study; analyzing of data; writing the first draft).

Chin-Mei Liu (developing the concept and design of the study; the analyses and interpretation of data; writing the first draft).

Charles Tzu-Chi Lee and Jie-Xi Hu equally contributed in this study.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Dr. Charles Tzu-Chi Lee, Jie-Xi Hu, and Dr. Chin-Mei Liu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2021.100707.

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