Postpancreatitis Diabetes Confers Higher Risk for Pancreatic Cancer Than Type 2 Diabetes: Results From a Nationwide Cancer Registry

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OBJECTIVE

Pancreatitis and diabetes are established risk factors for pancreatic cancer. However, to date, studies have investigated only the risk associated with either of them alone. The aim of this study was to investigate the effect of pancreatitis and diabetes combined, as well as their temporal relationship, on the risk of pancreatic cancer.

RESEARCH DESIGN AND METHODS

Nationwide cancer registry was linked to hospital discharge and mortality data from 1998 to 2015 in New Zealand. Incidence of primary pancreatic cancer in the four study groups (type 2 diabetes [T2D] alone, pancreatitis alone, T2D followed by pancreatitis, and postpancreatitis diabetes mellitus [PPDM]) was identified. Multivariable Cox regression analyses were conducted, with T2D as the reference group. A head-to-head comparison between the T2D followed by pancreatitis and PPDM groups was also performed.

RESULTS

Among 139,843 individuals (735,541 person-years), 913 (0.7%) were diagnosed with pancreatic cancer. The proportion of pancreatic cancer was 3.1%, 2.3%, 2.0%, and 0.6% in individuals with PPDM, T2D followed by pancreatitis, pancreatitis alone, and T2D alone, respectively. PPDM (hazard ratio [HR] 6.94; 95% CI 4.09–11.77) and T2D followed by pancreatitis (HR 5.35; 95% CI 3.52–8.14) were associated with significantly higher risks of pancreatic cancer compared with T2D alone. In the head-to-head comparison, PPDM was associated with a higher risk of pancreatic cancer compared with T2D followed by pancreatitis (HR 2.35; 95% CI 1.12–4.93).

CONCLUSIONS

Pancreatitis significantly increases the risk of pancreatic cancer in individuals with diabetes. In particular, PPDM poses the highest risk for pancreatic cancer.

Pancreatic cancer is one of the leading causes of cancer-specific mortality, with a 5-year survival rate of <10% (1), and it is projected to become the leading cause of cancer deaths by 2050 (2). Diabetes is often regarded as a risk factor for pancreatic cancer. A meta-analysis of 35 cohort studies reported that individuals with diabetes were at a 1.9-times-higher risk for pancreatic cancer compared with the risk for those

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without diabetes (3). Another established risk factor for pancreatic cancer is chronic pancreatitis. A meta-analysis of 13 studies showed that individuals with chronic pancreatitis were at a 7.9-times-higher risk for pancreatic cancer 5 years after the diagnosis of chronic pancreatitis (4). Acute pancreatitis is an emerging risk factor for pancreatic cancer, as suggested by two population-based studies from Denmark and Sweden in 2018 (5,6). The Danish study demonstrated that individuals with acute pancreatitis were at a 2.0-times-higher risk for pancreatic cancer compared with the age- and sex-matched general population without acute pancreatitis (6). The Swedish study showed that the risk of pancreatic cancer was 2.2 times higher in individuals with acute pancreatitis observed for 5–10 years and remained significantly higher after ruling out of the mediation effect of recurrence and chronicity of pancreatitis (5). Notably, all the previous studies were limited to investigating only one disease (either diabetes or pancreatitis) as a risk factor for pancreatic cancer. There is ample evidence that diabetes and pancreatitis are bidirectionally related (7,8). However, there is a dearth of evidence on the combined effect of diabetes and pancreatitis on the risk of pancreatic cancer.

A population-based study from the U.K. demonstrated that the incidence of diabetes of the exocrine pancreas was higher than that of adult-onset type 1 diabetes (9). The most common subtype of diabetes of the exocrine pancreas is diabetes following pancreatitis, termed postpancreatitis diabetes mellitus (PPDM), and it is observed in ~80% of individuals after pancreatitis (10). The study from the U.K. showed that PPDM is associated with poorer glycemic control compared with type 2 diabetes (T2D) (9). A 2019 population-based study from New Zealand demonstrated a significant mortality gap between individuals with PPDM and individuals with T2D, overall estimated at 14.8 excess deaths per 1,000 person-years in PPDM (11). This increased to 68 excess deaths per 1,000 person-years when the analysis was constrained to individuals who did not receive antidiabetes medications (12). It was also shown that cancer-related mortality was the second most common cause-specific mortality (following cardiovascular mortality) in individuals with PPDM (11). Moreover, individuals with PPDM (versus T2D) were at a 1.4-times-higher risk of cancer-related mortality—the single largest contributor to excess deaths (9.4 out of 14.8 per 1,000 person-years) (11). However, to date, no purposely designed study has investigated the risk of primary pancreatic cancer in PPDM versus T2D.

The aim of this study was to investigate whether diabetes and pancreatitis exert a combined effect on the risk of pancreatic cancer. Considering the presence or absence, as well as the sequences, of diabetes and pancreatitis, we explored the risk of primary pancreatic cancer in individuals with T2D alone, pancreatitis alone, T2D followed by pancreatitis, and PPDM.

RESEARCH DESIGN AND METHODS

Data Sources

The main data source was the New Zealand Cancer Registry (NZCR), a nationwide registry of all primary malignant diseases in the country. With use of a range of resources (laboratory data, mortality collection, and hospital discharge data), newly diagnosed cancer cases were routinely recorded along with the National Health Index number (assigned to every person who receives health care in New Zealand, which is publicly funded). The NZCR included diagnosis date, cancer site (based on ICD-9 and ICD-10 codes), and extent of disease (in situ, localized to organ of origin, invasion of adjacent tissue or organ, regional lymph nodes, and distant). For the purpose of this study, the NZCR database was linked to a hospital discharge database and a mortality database using de-identified encrypted National Health Index number (provided by the Ministry of Health Analytical Services). The hospital discharge database contained information on age, sex, ethnicity, area of residence, ICD codes of diseases and surgery, date of admission, and date of surgery. The study was exempt from ethics approval according to the Ministry of Health guidelines in New Zealand.

Study Cohort

Individuals who were first diagnosed with diabetes (ICD-10 E10, E11, E13) or pancreatitis (ICD-10 K85, K86.0, K86.1) were identified during the study period from 1 January 1998 to 31 December 2015. A 3-year washout period was applied (1995–1997) to ensure that these individuals were newly diagnosed. Individuals aged ≥55 years were included, as they are at risk for developing pancreatic cancer (1). The following four nonoverlapping groups were established: the T2D (T2D alone) group, the pancreatitis (PAN) group, the T2D-PAN group, and the PPDM group (Fig. 1). The T2D group was defined as individuals who were diagnosed with T2D (ICD-10 E11) and never with pancreatitis (ICD-10 K85, K86.0, K861) during the entire study period. The PAN group was defined as individuals who were diagnosed with acute pancreatitis (ICD-10 K85) or chronic pancreatitis (ICD-10 K86.0, K86.1) and never with diabetes (ICD-10 E10, E11, E13) during the entire study period (13). The T2D-PAN group was defined as individuals who were diagnosed with pancreatitis (ICD-10 K85, K86.0, K86.1) at least 90 days after first diagnosis of T2D (ICD-10 E11). In this group, none of the individuals had a record of pancreatitis diagnosis (ICD-10 K85, K86.0, K86.1) prior to or at the first diagnosis of T2D or within 90 days after it. The PPDM group was defined as individuals who were diagnosed with diabetes (ICD-10 E10, E11, E13) at least 90 days after first diagnosis of acute pancreatitis (ICD-10 K85) or chronic pancreatitis (ICD-10 K86.0, K86.1). The 90-day lag period was used to prevent the inclusion of patients with preexisting diabetes or stress-induced hyperglycemia (10,14,15). In this group, none of the individuals had a record of diabetes diagnosis (ICD-10 E10, E11, E13) prior to or at the first diagnosis of pancreatitis or within 90 days after it. Date of first diagnosis of diabetes (in the T2D and PPDM groups) or pancreatitis (in the PAN and T2D-PAN groups) was set as index date. Individuals with any cancer diagnosis (ICD-10 C00-D48) prior to or at the index date were excluded from all the groups.

Follow-up

The primary end point was incidence of primary pancreatic cancer. Any reported primary pancreatic cancer after the index date was considered as the event. Individuals with other cancers after the index date were censored (i.e., end of follow-up) at their first occurrence of cancer. To ensure the exclusion of pancreatic cancer from nonpancreas sites metastatic to the pancreas, we did not deem individuals with pancreatic cancer following other cancers (e.g., kidney, lung, stomach, colorectal,

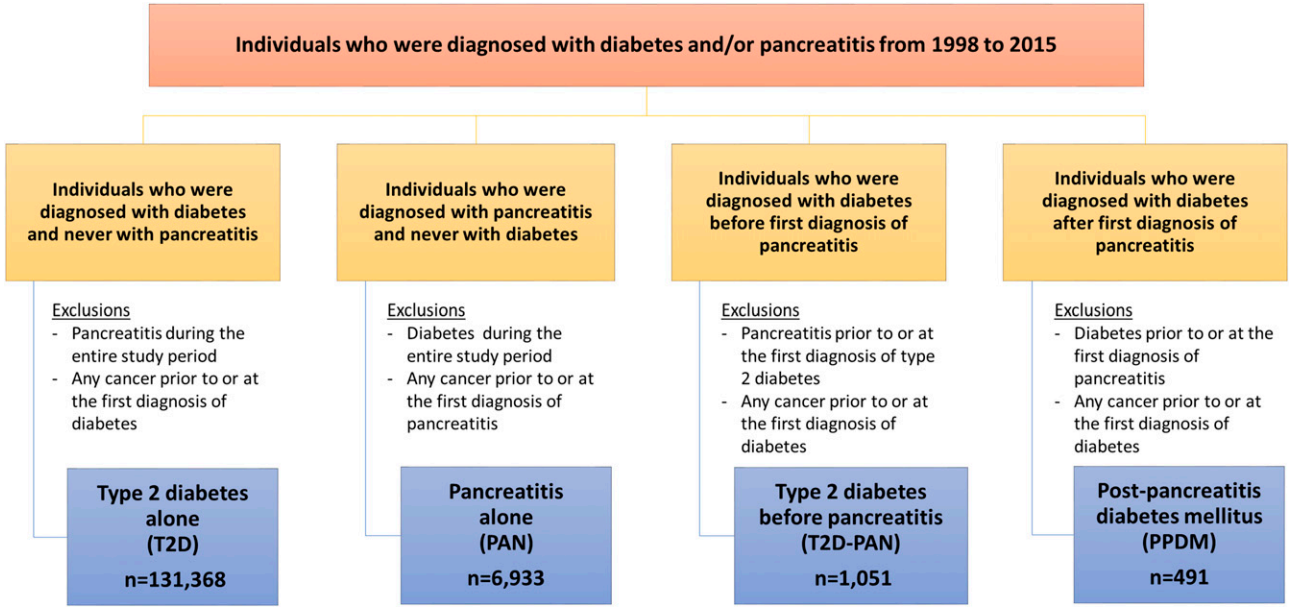

Figure 1—Selection process of the study groups.

prostate, breast, lymphoma, malignant melanoma) (16) to have primary pancreatic cancer. Individuals without any cancer after the index date were censored at death or the end of observation (31 December 2015)—whichever came first. The secondary end points were frequencies of metastatic, resected, and unresected cases of pancreatic cancer. This categorization was based on stage and resectability, in line with the National Comprehensive Cancer Network guidelines (17). Metastatic pancreatic cancer was identified based on the code of extent of disease (i.e., distant). The remaining cases were categorized as either resected or unresected pancreatic cancer. Resected pancreatic cancer was defined as the cases with at least one of the following surgery codes (ICD-10 3058300, 3058400, 3059300, 3059301) after the index date. Individuals who did not have the above surgery codes were categorized as unresected pancreatic cancer (17).

Covariates

Alcohol abuse (ICD-10 F10) and tobacco smoking (ICD-10 Z720, Z8643, Z87891) were defined based on the relevant ICD-10 codes during the entire study period (18). Ethnicity was classified as European, Māori or Pacific Islander, Asian, and others. Social deprivation index (based on area of residence) was classified into quartiles; individuals with missing values were categorized in an additional category (19). History of gallstones and cholecystectomy was defined as having the relevant diagnostic codes (ICD-10 K80, and K81 and 3044300, 3045401, 3045500, 3044500, 3044800, 3044900, and 3044600, respectively). The Charlson comorbidity index was calculated in line with the previous literature (20) and treated as a categorical variable (0, 1, 2, and $\geq$3).

Statistical Analysis

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Two-sided $P < 0.05$ was set as the threshold for statistical significance. One-way ANOVA (for age) and χ^2 tests (for the other variables) were conducted to examine differences in the characteristics between the four study groups. Crude and multivariable Cox regression analyses were conducted to estimate the risk of primary pancreatic cancer in the PAN group, the T2D-PAN group, and the PPDM group compared with the T2D group (the reference group). The multivariable Cox regression model included age, sex, ethnicity, social deprivation index, alcohol abuse, tobacco smoking, history of gallstones, cholecystectomy, and Charlson comorbidity index as covariates. The curves representing probability of developing pancreatic cancer were created after adjustment for all the covariates in the above Cox model. No violation of the proportionality assumption was confirmed by the log-likelihood ratio test in comparing of the fully adjusted model with the interaction term (group $\times$ follow-up days) and that without the interaction term. The risk of primary pancreatic cancer was expressed as hazard ratio (HR) with 95% CI.

Two additional analyses were performed. First, the above multivariable Cox regression analysis was repeated after truncation of the follow-up period ($<$12 months and $\geq$12 months) in the T2D and PPDM groups. This analysis enabled us to examine the possible impact of reverse causality between diabetes and pancreatic cancer. It also enabled us to investigate the possible impact of diabetes duration on the studied association (as the follow-up period was identical to diabetes duration in the T2D and PPDM groups). The selection of the 12-month lag period was justified by the findings of a study that showed the presence of up to 12 months of lead time between diagnosis of diabetes and diagnosis of pancreatic cancer (21). Second, a head-to-head comparison between the T2D-PAN and PPDM groups was conducted. The risk of primary pancreatic cancer was estimated using the above multivariable Cox regression model (with the T2D-PAN group as the reference group) after exclusion of individuals with diagnosis of pancreatic cancer within 12 months after first diagnosis of

pancreatitis (5). This analysis enabled us to investigate the impact of the temporal relationship between diabetes and pancreatitis on the risk of pancreatic cancer.

RESULTS

Characteristics of Study Individuals

A total of 139,843 individuals were observed for a mean ± SD period of 5.3 ± 4.6 years. Mean age was 70.4 ± 9.4 years in the T2D group (n = 131,368), 70.7 ± 10.1 years in the PAN group (n = 6,933), 68.0 ± 8.2 years in the T2D-PAN group (n = 1,051), and 68.9 ± 9.4 years in the PPDM group (n = 491). Men accounted for 50.9%, 48.5%, 58.4%, and 60.1% in the T2D group, the PAN group, the T2D-PAN group, and the PPDM group, respectively. The average duration of diabetes was 5.3 years in the T2D group, 8.3 years in the T2D-PAN group, and 3.4 years in the PPDM group. Other characteristics are presented in Table 1.

Table 1—Characteristics of the study groups

	T2D	PAN	T2D-PAN	PPDM	*P*
n	131,368	6,933	1,051	491	
Age (years), mean (SD)	70.4 (9.4)	70.7 (10.1)	68.0 (8.2)	68.9 (9.4)	<0.001
Men, *n* (%)	66,866 (50.9)	3,365 (48.5)	614 (58.4)	295 (60.1)	<0.001
Ethnicity, *n* (%)					
European	85,287 (64.9)	5,664 (81.7)	606 (57.7)	371 (75.6)	<0.001
Māori or Pacific Islander	27,565 (21.0)	720 (10.4)	310 (29.5)	85 (17.3)	
Asian	10,151 (7.7)	212 (3.1)	71 (6.8)	20 (4.1)	
Other	8,365 (6.4)	337 (4.9)	64 (6.1)	15 (3.1)	
Social deprivation index, *n* (%)					
Quartile 1	28,816 (21.9)	1,857 (26.8)	184 (17.5)	96 (19.6)	<0.001
Quartile 2	36,750 (28.0)	2,062 (29.7)	268 (25.5)	139 (28.3)	
Quartile 3	15,968 (12.2)	886 (12.8)	145 (13.8)	74 (15.1)	
Quartile 4	38,438 (29.3)	1,592 (23.0)	352 (33.5)	145 (29.5)	
Missing	11,396 (8.7)	536 (7.7)	102 (9.7)	37 (7.5)	
Alcohol abuse, *n* (%)	2,692 (2.1)	460 (6.6)	85 (8.1)	55 (11.2)	<0.001
Tobacco smoking, *n* (%)	66,935 (51.0)	2,791 (40.3)	721 (68.6)	323 (65.8)	<0.001
History of gallstones, *n* (%)	35 (0.0)	60 (0.9)	138 (13.1)	58 (11.8)	<0.001
Cholecystectomy, *n* (%)	15 (0.0)	9 (0.1)	37 (3.5)	33 (6.7)	<0.001
Charlson comorbidity index, *n* (%)					
0	0 (0.0)	5,594 (80.7)	0 (0.0)	0 (0.0)	<0.001
1	61,437 (46.8)	757 (10.9)	549 (52.2)	220 (44.8)	
2	21,993 (16.7)	323 (4.7)	177 (16.8)	75 (15.3)	
≥3	47,938 (36.5)	259 (3.7)	325 (30.9)	196 (39.9)	

P values were from one-way ANOVA (for age) and χ^2 tests (for the other variables) between the four groups. Tobacco smoking and alcohol abuse were identified throughout the entire observation period.

Incidence of Primary Pancreatic Cancer in the Study Groups

The number of individuals with primary pancreatic cancer was 913 (0.7%) in the overall cohort. The proportion of pancreatic cancer was 3.1%, 2.3%, 2.0%, and 0.6% in the PPDM group, the TD2-PAN group, the PAN group, and the T2D group, respectively. The probability of developing pancreatic cancer was the highest in the PPDM group in both crude and adjusted analyses (Fig. 2). The PPDM group had a significantly higher risk of pancreatic cancer compared with the T2D group (adjusted HR 6.94; 95% CI 4.09–11.77) (Table 2). The T2D-PAN group had a significantly higher risk of pancreatic cancer compared with the T2D group (adjusted HR 5.35; 95% CI 3.52–8.14). In the analysis after truncation of the follow-up period, the higher risk of pancreatic cancer associated with the PPDM group (versus the T2D group) remained statistically significant both in individuals with <12 months of follow-up (adjusted HR 3.95; 95% CI 1.90–8.18) and those with ≥12 months of follow-up (adjusted HR 7.93; 95% CI 3.53–17.81). In the head-to-head comparison, the PPDM group had a significantly higher risk of pancreatic cancer compared with the T2D-PAN group (adjusted HR 2.35; 95% CI 1.12–4.93).

Stage and Resectability of Primary Pancreatic Cancer in the Study Groups

The proportions of metastatic, unresected, and resected cases were 50.1% (n = 457), 43.8% (n = 400), and 6.1% (n = 56), respectively. The proportion of metastatic pancreatic cancer was 1.4%, 1.3%, 0.9%, and 0.3% in the PPDM group, the TD2-PAN group, the PAN group, and the T2D group, respectively. The PPDM group had significantly higher risks of metastatic pancreatic cancer (adjusted HR 6.80; 95% CI 3.17–14.61), resected pancreatic cancer (adjusted HR 17.66; 95% CI 4.11–75.89), and unresected pancreatic cancer (adjusted HR 5.70; 95% CI 2.42–13.45) compared with the T2D group. Other comparisons are presented in Table 2.

CONCLUSIONS

Using a nationwide cohort with an up to 18-year observation period, we investigated, for the first time, the risk of primary pancreatic cancer in individuals with T2D alone, pancreatitis alone, T2D followed by pancreatitis, and PPDM. The linkage of nationwide cancer registry, hospital discharge data, and mortality data enabled us to obtain comprehensive data on primary pancreatic cancer, hence ensuring greater generalizability. In addition, we addressed the possible issue of reverse causality by introducing a 12-month lag period between diabetes diagnosis and pancreatic cancer diagnosis into the analysis. After adjustment for a number of relevant covariates, individuals with PPDM and those with T2D followed by pancreatitis had 6.9 times and 5.4 times significantly higher risks of pancreatic cancer than individuals with T2D alone, respectively. This suggests that the development of pancreatitis considerably increases the risk for pancreatic cancer in individuals with diabetes. Moreover, given that individuals with diabetes after pancreatitis were at a 2.3 times significantly higher risk for pancreatic cancer than those with diabetes before pancreatitis (after adjustment for covariates), the temporal relationship between diabetes and pancreatitis appears to be important.

It is noteworthy that individuals with PPDM had the highest risk of pancreatic cancer among all the study groups. One could argue that the increased risk of pancreatic cancer in individuals with PPDM might have been due to the

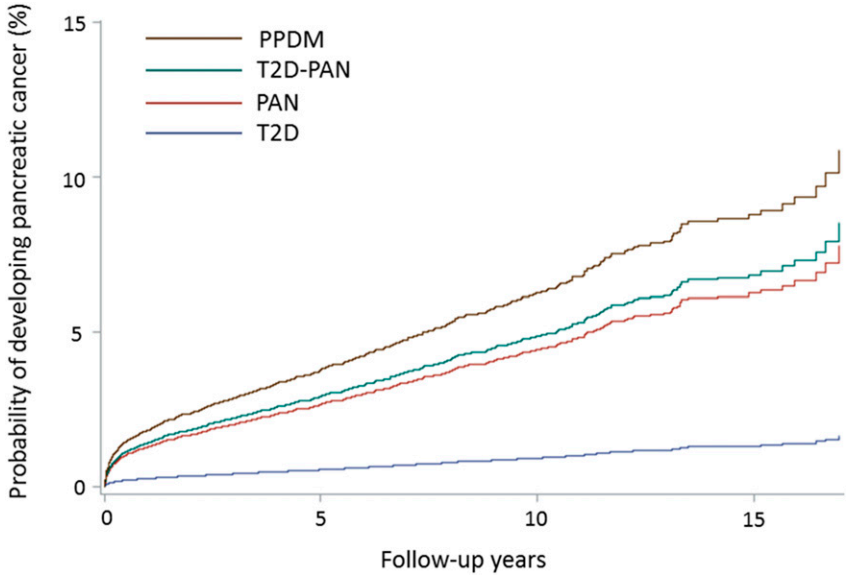

Figure 2—Probability of developing pancreatic cancer in the study groups. The analysis was adjusted for age, sex, ethnicity, social deprivation index, alcohol abuse, tobacco smoking, history of gallstones, cholecystectomy, and Charlson comorbidity index.

effect of pancreatitis merely as a comorbidity in individuals with diabetes. However, the head-to-head comparison showed that the risk of pancreatic cancer in the PPDM group was significantly higher than that in the T2D-PAN group (even after adjustment for covariates). This means that an attack of pancreatitis in individuals with diabetes has a differential effect on the subsequent risk of pancreatic cancer depending on whether it occurs before or after diabetes. Unfortunately, the management of diabetes of the exocrine pancreas is not standardized and none of the current diabetes treatment guidelines specifically focus on PPDM. Empirical data indicate that antidiabetes medications (specifically, metformin) are administered disproportionately in PPDM versus T2D and this might contribute to the differing risk for pancreatic cancer. A 2019 population-based study showed that the proportion of metformin ever users was lower in individuals with PPDM (59.6%) versus T2D (74.1%) (12). This is important as a 2014 meta-analysis of 13 studies demonstrated that metformin was associated with a 37% reduced risk of pancreatic cancer in individuals with T2D (22). However, the included primary studies were generally of low methodological quality. Further, several methodologically robust studies published in recent years were unable to demonstrate a beneficial effect of metformin in pancreatic cancer (23,24). Purposely designed and adequately powered studies are now warranted to investigate whether the use of metformin significantly affects the risk for primary pancreatic cancer specifically in those individuals with diabetes who have a history of pancreatitis.

The increased risk of primary pancreatic cancer associated with PPDM indicates that pancreatitis exerts an effect beyond being a comorbidity in individuals with PPDM and it can be attributed to at least two factors. One explanation is that poorer glycemic control may play a role in heightening the risk of pancreatic cancer in individuals with PPDM versus T2D. A 2017 population-based study observed 31,789 individuals with adult-onset diabetes and found that individuals with PPDM were at a 1.7-times-higher risk of poor glycemic control (defined as HbA_{1c} $\geq$7% [53 mmol/mol]) compared with those with T2D (9). This finding is of importance because higher HbA_{1c} in individuals with diabetes is associated with greater risk of pancreatic cancer, as demonstrated in a 2015 matched case-control study of 4,301 individuals with diabetes (25). It is also possible that PPDM, as a distinct type of diabetes, has some pathophysiological characteristics that inherently increase the risk of primary pancreatic cancer. For example, emerging evidence suggests that intrapancreatic fat deposition (IPFD) is a risk factor for pancreatic cancer. This possibly involves two mechanisms: intrapancreatic fat accumulation resulting from expanding visceral fat and intrapancreatic fat replacement triggered by acinar-to-adipocyte transdifferentiation (due to factors such as *c-Myc, Gata6,* periostin) following recurrent attacks of pancreatitis (26). It is hypothesized that the former is present in both T2D and PPDM, whereas the latter is present in PPDM only (14). However, although recent studies have provided valuable insights into the mechanisms of IPFD following pancreatitis (27–31), no purposely designed study has investigated the difference in IPFD between PPDM and T2D. Future investigations should clarify the intricate relationship between PPDM, IPFD, and pancreatic cancer.

The current study adds to the debate over early detection of pancreatic cancer. Given that the overwhelming majority of pancreatic cancer is unresectable at the time of diagnosis, early detection of pancreatic cancer could enable the administration of curative treatment (e.g., pancreatic surgery) and, hence, improve the prognosis of pancreatic cancer (32). However, a 2019 evidence-based report by the U.S. Preventive Services Task Force did not recommend screening for pancreatic cancer in asymptomatic adults because of limited evidence on cost-effectiveness of this approach (33). Although numerous studies have suggested that T2D is a risk factor for pancreatic cancer (3), they did not comprehensively consider history of pancreatitis. Notably, the current study showed that the proportions of overall pancreatic cancer (0.6%) and metastatic pancreatic cancer (0.3%) were lowest in the T2D group. This brings up the question of whether T2D in itself is indeed a risk factor for pancreatic cancer or, rather, an amplifier of other risk factors (such as pancreatitis). In the current study, the probability of developing pancreatic cancer in individuals with pancreatitis following T2D was similar to that in individuals with pancreatitis alone (Fig. 2). This suggests that T2D in itself is not a major risk factor for pancreatic cancer in individuals with pancreatitis. By contrast, pancreatitis is a major risk factor for pancreatic cancer in individuals with diabetes. In the current study, post–acute pancreatitis diabetes was

Table 2—Risk of pancreatic cancer in the study groups

	Person-years	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall pancreatic cancer			
T2D	694,503	1.00	1.00
PAN	35,313	3.63 (3.03–4.36)	4.86 (3.38–6.99)
T2D-PAN	4,062	5.03 (3.35–7.55)	5.35 (3.52–8.14)
PPDM	1,662	7.17 (4.30–11.96)	6.94 (4.09–11.77)
Resected pancreatic cancer			
T2D	694,503	1.00	1.00
PAN	35,313	10.97 (6.16–19.54)	18.88 (6.51–54.75)
T2D-PAN	4,062	17.97 (6.35–50.90)	16.11 (5.48–47.36)
PPDM	1,662	19.45 (4.66–81.26)	17.66 (4.11–75.89)
Unresected pancreatic cancer			
T2D	694,503	1.00	1.00
PAN	35,313	3.51 (2.66–4.63)	3.41 (1.86–6.26)
T2D-PAN	4,062	2.84 (1.27–6.36)	2.87 (1.24–6.60)
PPDM	1,662	6.53 (2.91–14.65)	5.70 (2.42–13.45)
Metastatic pancreatic cancer			
T2D	694,503	1.00	1.00
PAN	35,313	3.12 (2.37–4.09)	5.32 (3.21–8.83)
T2D-PAN	4,062	5.77 (3.38–9.83)	6.53 (3.78–11.28)
PPDM	1,662	6.57 (3.11–13.88)	6.80 (3.17–14.61)

Adjusted HRs were from multivariable Cox regression models including age, sex, ethnicity, social deprivation index, alcohol abuse, tobacco smoking, history of gallstones, history of cholecystectomy, and Charlson comorbidity index.

associated with 5.0 times significantly higher risk (adjusted HR 5.08; 95% CI 2.49–10.33) and post–chronic pancreatitis diabetes was associated with 12.0 times significantly higher risk (adjusted HR 11.95; 95% CI 5.59–25.53) for pancreatic cancer compared with T2D. Moreover, individuals with PPDM were at a 4.0-times-higher risk for pancreatic cancer compared with those with T2D when the follow-up period was constrained to <12 months. Individuals who developed pancreatic cancer during this 12-month period may have had presymptomatic pancreatic cancer at diagnosis of diabetes, and new-onset diabetes may have been an early marker of pancreatic cancer. Hence, PPDM could be a stronger harbinger of pancreatic cancer than T2D. Studies on early detection of pancreatic cancer in the ensuing decennia may benefit if history of acute or chronic pancreatitis, as well as the sequences of pancreatitis and T2D, are taken into account.

There are further points to consider when interpreting our findings. First, the current study used hospital discharge data to identify individuals with diabetes, whereas diabetes is often first diagnosed in primary care. This approach was chosen to obtain an appropriate comparator (such as hospitalized individuals) for individuals with pancreatitis, who almost invariably require hospital admission. It is worth noting that we identified diabetes using diagnostic codes in both primary and (up to 20) secondary positions. This means that not all included individuals with the diabetes codes were hospitalized for diabetes. Further, given that individuals with T2D managed in primary care only are more likely to have mild diabetes (and, hence, have a lower risk of pancreatic cancer, as the levels of hyperglycemia and the risk for pancreatic cancer are directly associated in individuals with diabetes [21]), our approach likely resulted in conservative risk estimates. Second, data on histological types of pancreatic cancer were incomplete, which was similar to several published population-based studies on pancreatic cancer from other countries (6,25). It is known that pancreatic ductal adenocarcinoma represents >90% of pancreatic cancer (32), and a population-based study from Sweden on acute pancreatitis as a risk factor for pancreatic cancer reported no substantial difference in their sensitivity analysis constrained to pancreatic ductal adenocarcinoma (5). Third, the category of individuals with unresected pancreatic cancer might have included those who had potentially resectable cases but did not undergo surgery because of comorbidities or patient choice. We did not have access to information about operability and patient preferences; hence, further categorization of unresected pancreatic cancer was not possible. Fourth, there might have been unmeasured confounders such as excess adiposity—a causal risk factor for pancreatic cancer (32,34). However, the frequency of obesity was higher in individuals with T2D (48%) versus PPDM (35%) in a population-based study from the U.K. (9). This suggests that the risk for pancreatic cancer associated with PPDM observed in the current study is likely to be conservative. Fifth, alcohol abuse and tobacco smoking were identified using diagnostic codes, which might have led to a misclassification bias. However, if there had been a misclassification, it would have been a nondifferential misclassification, as the study groups were derived from a single hospitalization cohort (covering the entire country with a unitary health care system) and the alcohol/tobacco variables were identified using the same automated method and were independent of the study groups. It is known that nondifferential misclassification can only bias an estimate of a true positive HR downward and not away from or beyond the null value (35,36). Furthermore, given that lifestyle factors are underreported in most administrative databases (2), we identified the alcohol/tobacco variables throughout the entire observation period (hence, presenting data on ever smokers and ever alcohol abusers). Last, one could argue that the results of the current study from New Zealand may not be generalizable to other geographical areas. However, from the global perspective, the incidence of pancreatic cancer in New Zealand is similarly high compared with that in the U.S. (37). Further, while African Americans are a high-risk group for pancreatic cancer in the U.S., Māori people are a high-risk group for pancreatic cancer in New Zealand (38).

In conclusion, an attack of pancreatitis in individuals with diabetes significantly increases the risk for primary pancreatic cancer. Moreover, the temporal relationship between diabetes and pancreatitis is not negligible, as pancreatitis preceding diabetes is a stronger risk factor for pancreatic cancer than pancreatitis following diabetes. The mechanisms underlying this observation warrant purposely designed studies.

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Author Contributions. J.C. and M.S.P. designed the study. J.C. analyzed data and drafted the manuscript. R.S. and M.S.P. provided significant intellectual input and critical review of the manuscript. M.S.P. supervised the study. All authors approved the final version of this manuscript. M.S.P. is the guarantor of this work and, as such, 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.

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