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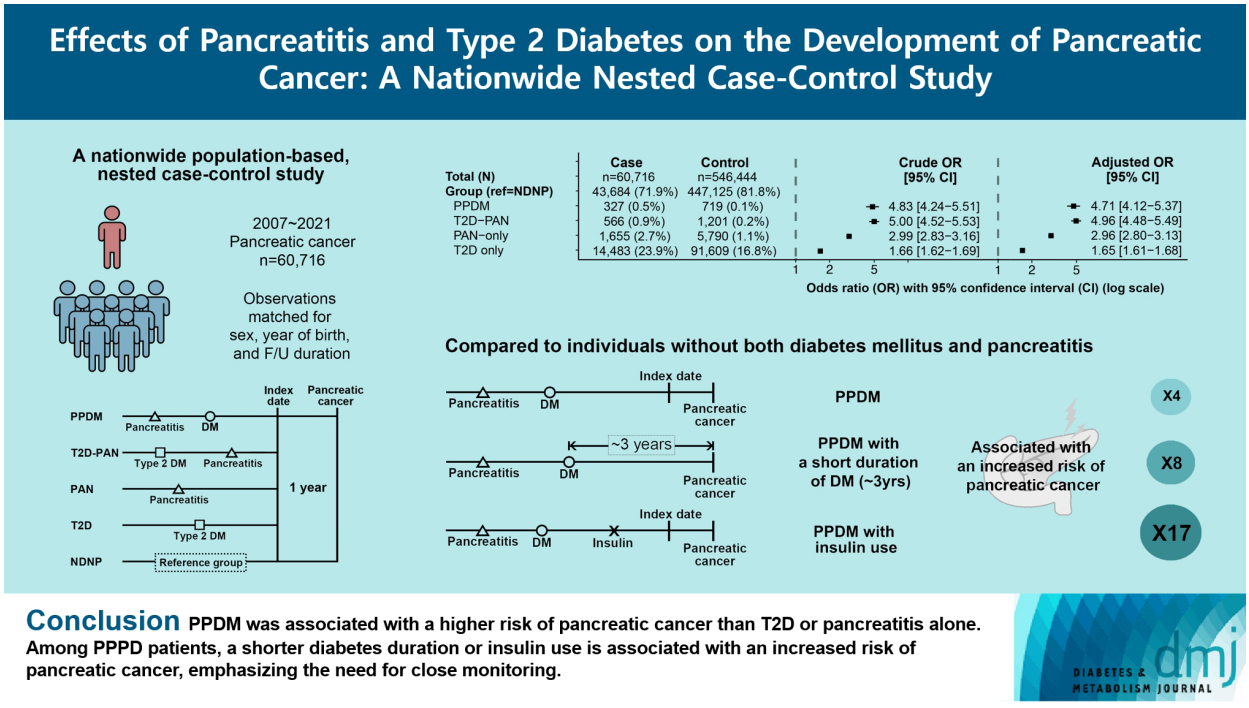

Highlights

- **PPDM had a higher pancreatic cancer risk than T2D or pancreatitis alone.**
- **Among PPDM patients, shorter DM duration or insulin use conferred an elevated risk.**
- **These findings highlight the need for close monitoring in high-risk PPDM groups.**

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Effects of Pancreatitis and Type 2 Diabetes Mellitus on the Development of Pancreatic Cancer: A Nationwide Nested Case-Control Study

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Background: Despite diabetes mellitus (DM) and pancreatitis being known risk factors for pancreatic cancer, patients with these conditions are not included in pancreatic cancer screening due to the low incidence of pancreatic cancer in these populations. This study aimed to determine the high-risk subgroup of patients with diabetes and pancreatitis that would benefit from pancreatic cancer screening.
Methods: A nested case-control study was conducted using data from the National Health Information Database of the Korean National Health Insurance Service. Patients were categorized into the following groups: type 2 diabetes mellitus only (T2DM-only), pancreatitis-only (PAN-only), T2DM followed by pancreatitis (T2DM-PAN), post-pancreatitis diabetes mellitus (PPDM), and no diabetes and no pancreatitis (NDNP). Conditional logistic regression was used to determine significant associations of each group with pancreatic cancer development risk.
Results: The risk of pancreatic cancer was significantly higher in the T2DM-PAN (adjusted odds ratio [AOR], 4.96; 95% confidence interval [CI], 4.48 to 5.49) and PPDM (AOR, 4.71; 95% CI, 4.12 to 5.37) groups than in the NDNP group. Compared to patients in the NDNP group, those with PPDM using insulin had a 17-fold increased risk (AOR, 16.72; 95% CI, 9.50 to 29.43), and individuals with PPDM who had diabetes for less than 3 years had a more than 8-fold increased risk of pancreatic cancer (AOR, 8.83; 95% CI, 5.99 to 13.01).
Conclusion: In patients with post-pancreatitis diabetes, insulin use or shorter duration of diabetes was associated with a higher risk of pancreatic cancer, suggesting that patients in these subgroups may require close monitoring for pancreatic cancer development.

Keywords: Diabetes mellitus, type 2; Pancreatitis; Pancreatic neoplasms

INTRODUCTION

Pancreatic cancer was ranked twelfth in terms of incidence (495,773 new cases), but was the seventh leading cause of cancer mortality (466,003 deaths) worldwide in 2020 [1]. In South Korea, cancer has emerged as the leading cause of death among patients with diabetes, accounting for about 30% of all deaths [2], and in the overall population, pancreatic cancer was the eighth most commonly diagnosed cancer (8,414 new cases), with the fifth highest age-standardized cancer mortality rate (5.7 per 100,000) in 2020 [3]. The Surveillance, Epidemiology, and End Results (SEER) 5-year relative survival rates for pancreatic cancer during 2013–2019 were 44.3%, 16.2%, and 3.2% for localized, regional, and distant stages, respectively, with the survival rates declining sharply as the staging progressed [4]. In most cases, pancreatic cancer is diagnosed at the distant

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stage, while only some cases are diagnosed at the local stage (13.0%) [3,4]. One of the reasons pancreatic cancer has one of the highest mortality rates is that, it is mostly diagnosed in advanced stages owing to the lack of effective screening strategies.

Although diabetes [5-7] and pancreatitis [8-13] are known risk factors for pancreatic cancer, current guidelines do not recommend aggressive screening in patients with diabetes or pancreatitis because pancreatic cancer screening is specifically recommended for high-risk populations, including individuals with a >5% lifetime risk or a relative risk increased by more than 5-fold compared to the general population [14,15]. Previous studies on the risk factors for pancreatic cancer have attempted to simultaneously analyze diabetes and pancreatitis [16-18]. Population-based cohort studies in Taiwan found that patients with both diabetes and chronic pancreatitis had a significantly increased risk of pancreatic cancer compared to those with neither disease [16,18]. Another population-based cohort study in South Korea found that patients with acute pancreatitis had a higher risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) [19]. In addition, a study based on the nationwide cancer registry in New Zealand reported that post-pancreatitis diabetes mellitus (PPDM) was associated with a significantly higher risk of pancreatic cancer than T2DM alone [17]. Although previous studies provide important insights, these studies either did not consider the sequential occurrence of diabetes and pancreatitis or lacked comparisons with the general population.

This nationwide, population-based study pursued three main objectives: (1) to examine the combined effect of pancreatitis and diabetes on the risk of pancreatic cancer relative to their absence; (2) to determine if the sequence of onset between diabetes and pancreatitis influences the risk of pancreatic cancer; and (3) to pinpoint high-risk subgroups for pancreatic cancer, for whom screening might be advised.

METHODS

Data sources

The data used in the current study were extracted from the National Health Information Database (NHID) of the Korean National Health Insurance Service (NHIS) for the period between 2002 and 2021 [20]. The Korean NHID contains nationwide claims and health examination data [21]. The NHIS, as the single insurer, pays health care costs based on the billing records of health care providers [20]. The NHIS covers almost the entire population of South Korea, with over 50 million individuals as of 2020 [22]. The NHID provides researchers with a platform for using customized retrospective cohort data [23]; moreover, it contains information on income-based insurance contributions, demographic variables, and date of death, as well as information regarding records on inpatient and outpatient usage (diagnosis codes, hospital admission, and special reimbursement codes) and medical treatment (prescriptions and procedures) from January 2002 to December 2021 [23]. This study adhered to the ethical standards set forth in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of Yonsei University College of Medicine (No. 4-2021-1489). Given the use of de-identified data from a national database, the IRB granted a waiver of informed consent.

Study population

Data were collected from 2002 to 2021, but because of a 5-year washout period, we enrolled patients newly diagnosed with pancreatic cancer from 2007 to 2021 as the case group and matched patients who did not develop pancreatic cancer as the control group. The following exclusion criteria were applied: (1) diagnostic code of C254 (malignant neoplasm of endocrine pancreas); (2) history of any type of cancer (International Classification of Diseases, 10th Revision [ICD-10]: C00-97) in the 3 years prior to the date of pancreatic cancer diagnosis; (3) missing data (body mass index [BMI], alcohol consumption, and smoking); (4) type 1 diabetes mellitus (T1DM) (ICD-10: E10) without pancreatitis or T1DM prior to pancreatitis; and (5) concurrent diagnosis of diabetes and pancreatitis within 3 months before the index date or hospital visit in 2002 for both chronic pancreatitis and diabetes. Because the database did not contain claims data prior to 2002, it was not possible to determine which disease preceded the other.

For the selection of case observations, we first selected patients with newly diagnosed pancreatic cancer from 2007 to 2021 and excluded those who met the exclusion criteria. Then, we matched 60,716 patients with pancreatic cancer to 6,071,491 observations without pancreatic cancer (control) by birth, sex, and length of follow-up at a ratio of 1:100. After incidence density sampling, we excluded observations in the control group who met the exclusion criteria and conducted simple random sampling at a ratio of 1:9. Finally, the control group included 546,444 observations (Fig. 1).

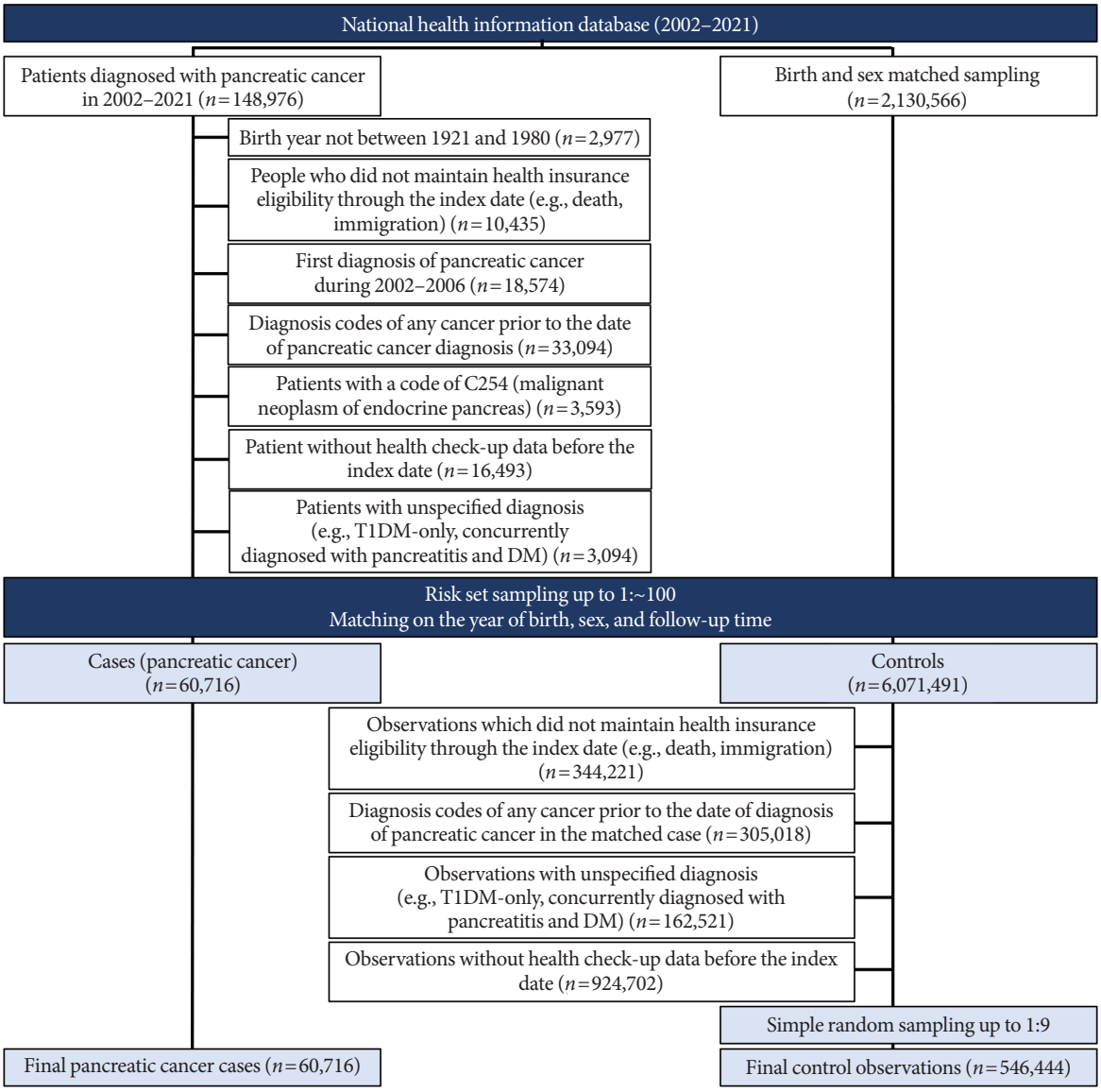

Fig. 1. Flowchart of the study inclusion and exclusion criteria. T1DM, type 1 diabetes mellitus; DM, diabetes mellitus.

Clinical variables

Diagnosis of diabetes and pancreatitis was only considered if they occurred before the index date. We defined the index date as 1 year prior to the date of diagnosis of pancreatic cancer because pancreatitis and hyperglycemia can be symptoms of pancreatic cancer development [24,25]. Although the index date was set as 1 year prior to the date of diagnosis of pancreatic cancer for the main analyses, in the analysis that further divided the groups according to diabetes mellitus (DM) duration and pancreatitis duration, the index date was defined as the date of diagnosis of pancreatic cancer to include new-onset disease.

Pancreatic cancer was defined when ICD-10 code C25 and special reimbursement code V193 were recorded simultaneously. The NHID started using special reimbursement codes (V193 codes) since September 2005 to reduce the copayment rate to 5% for cancers. In order to register a cancer patient under the V193 code, the diagnosis must be confirmed by a test (such as histologic, cytologic, biochemical, immunohistochemical, hematologic, imaging, or diagnostic surgery) based on the criteria established by the Ministry of Health and Welfare. Therefore, the use of ICD-10 C-codes and V193 codes al-

lows for an accurate definition of cancer.

Patients were deemed to have diabetes if glucose-lowering medications were prescribed and the ICD-10 code for diabetes (ICD-10: E10-14) was present in inpatient or outpatient NHIS claims data [26]. Patients with T2DM were defined as patients without a T1DM diagnosis code (ICD-10: E10) before the index date in predefined patients with diabetes. Pancreatitis was confirmed when the ICD-10 code for pancreatitis was used, when acute pancreatitis (ICD-10: K85) was the principal diagnosis or first-to-fourth additional diagnosis on at least one inpatient NHIS claim, or when chronic pancreatitis was stated (ICD-10: K86.0 and K86.1) on at least one inpatient or more than two outpatient NHIS claims.

We divided the patients into five non-overlapping groups based on the grouping in a previous study [17,27,28]. The T2DM-alone (T2DM-only) group included the patients who were diagnosed with T2DM and had never been diagnosed with pancreatitis prior to the index date. The pancreatitis-only (PAN-only) group included patients who were diagnosed with pancreatitis and had never been diagnosed with diabetes prior to the index date. Patients with both diabetes and pancreatitis prior to the index date were divided into two groups based on the sequence of disease onset and type of diabetes. The pancreatitis after T2DM (T2DM-PAN) group included those who were diagnosed with pancreatitis at least 90 days after diagnosis of T2DM. The PPDM group included those who were diagnosed with diabetes (ICD-10: E10-14) at least 90 days after the first diagnosis of pancreatitis. Those who did not fall into any of the above four disease categories were categorized into the no diabetes and no pancreatitis (NDNP) group.

Smoking status was classified as current, past, or non-smokers based on participants' responses to the health screening questionnaire. Alcohol consumption was estimated based on survey responses, calculated in grams per week, converted to standard drinks (14 g of alcohol per drink), and categorized as 'heavy drinking' if men consumed 15 or more drinks per week and women 8 or more [29].

The risk of pancreatic cancer for each subgroup was analyzed. The PPDM, T2DM-PAN, and T2DM-only groups were further stratified based on insulin use into continuous, temporary, and non-user categories. Continuous insulin users were defined as those who received a minimum of five insulin prescriptions within the 3 years preceding the index date (for hospitalizations, multiple prescriptions during a single admission were counted as one instance). Temporary insulin users were defined as those who had received at least one insulin prescription but did not fulfill the criteria for continuous use. Furthermore, we conducted a sensitivity analysis by redefining the continuous insulin user criteria as receiving insulin prescriptions either (1) at least three times or (2) at least twice within the 3 years prior to the index date.

Additional analyses for the duration of diabetes and pancreatitis were performed by only including diabetes and pancreatitis cases diagnosed after 2004 to include subjects for whom the exact duration of diabetes and pancreatitis could be accurately determined, and by using the index date as the date of pancreatic cancer diagnosis (without lag period) to include new-onset DM and new-onset pancreatitis cases with a duration of less than 1 year.

Sensitivity analysis

To minimize the potential impact of reverse causality, a 1-year lag period was applied when setting the index date in the main analysis. Additionally, we conducted a sensitivity analysis using various lag periods (0, 0.5, 1, 2, 3, and 5 years) to evaluate whether the outcomes were influenced by the length of the lag period. Additionally, we performed another sensitivity analysis by excluding individuals who had undergone pancreatectomy prior to the index date.

Statistical analysis

We first compared the baseline characteristics of case and control groups based on the diagnosis, using chi-square tests for categorical variables and *t*-tests for continuous variables. Baseline characteristics consisting of continuous variables were presented as mean±standard deviation, and categorical variables were presented as number (%).

We performed the analyses using a conditional logistic regression model to determine whether T2DM-only, PAN-only, T2DM-PAN, or PPDM status was associated with a higher risk of pancreatic cancer than that related to the NDNP status. Multiple logistic regression was performed using BMI, tobacco use, and alcohol consumption as variables. We used SAS version 9.3 (SAS Institute, Cary, NC, USA) for data analysis.

RESULTS

Baseline characteristics

As shown in Table 1, in the majority of the cases, pancreatic cancer was diagnosed in people aged >70 years, and men were

more frequently diagnosed with pancreatic cancer than women (54.5% vs. 45.5%). The proportion of heavy drinkers (7.3% vs. 6.6%) and current smokers (22.1% vs. 16.8%) was higher in the pancreatic cancer group than in the control group. The difference in the mean BMIs of the case and control groups was statistically significant, but the mean BMIs were numerically similar at 24.1 and 24.0 (Table 1). In all groups except the NDNP group, the mean age was higher in the non-pancreatic cancer group, whereas the percentage of older adults was lower in the pancreatic cancer group compared to the control group (Supplementary Tables 1 and 2).

Table 1. Baseline demographic and clinical characteristics of patients with pancreatic cancer and matched controls

Variable	Case (n=60,716)	Control (n=546,444)	P value
Age at index date, yr	69±11	69±11	1.000
<40	337 (0.6)	3,033 (0.6)	
≥40 and <50	2,945 (4.9)	26,505 (4.9)	
≥50 and <60	9,514 (15.7)	85,626 (15.7)	
≥60 and <70	17,068 (28.1)	153,612 (28.1)	
≥70 and <80	20,048 (33.0)	180,432 (33.0)	
≥80	10,804 (17.8)	97,236 (17.8)	
Sex			
Male	33,085 (54.5)	297,765 (54.5)	1.000
Female	27,631 (45.5)	248,679 (45.5)	
Smoking			<0.001[a]
Non-smoker	37,550 (61.8)	359,010 (65.7)	
Past-smoker	9,773 (16.1)	95,466 (17.5)	
Current smoker	13,393 (22.1)	91,968 (16.8)	
Alcohol consumption			<0.001[a]
Light or non-drinker	47,313 (77.9)	431,674 (79.0)	
Moderate drinker	8,949 (14.7)	78,949 (14.4)	
Heavy drinker	4,454 (7.3)	35,821 (6.6)	
BMI, kg/m^2	24.1±3.2	24.0±3.2	0.005[a]
<18.5	1,960 (3.2)	16,750 (3.1)	<0.001[a]
18.5–<25	36,131 (59.5)	329,157 (60.2)	
25–<30	20,164 (33.2)	180,502 (33.0)	
≥30	2,461 (4.1)	20,035 (3.7)	

Values are presented as mean±standard deviation or number (%). Statistical comparisons were performed using the t-test for continuous variables and the chi-square test for categorical variables.
BMI, body mass index.
[a]P<0.05.

Association of DM and/or pancreatitis with pancreatic cancer risk

In the conditional logistic regression analysis, PPDM and T2DM-PAN were significantly associated with pancreatic cancer, with higher odds ratios than those for the T2DM-only and PAN-only groups. In the simple logistic regression, the adjusted odds ratios (AORs) were significantly higher in the T2DM-only (AOR, 1.65; 95% confidence interval [CI], 1.61 to 1.68), PAN-only (AOR, 2.96; 95% CI, 2.80 to 3.13), T2DM-PAN (AOR, 4.96; 95% CI, 4.48 to 5.49), and PPDM (AOR, 4.71; 95% CI, 4.12 to 5.37) groups than in the NDNP group (Fig. 2, Supplementary Table 3). Both being a current smoker and having a heavy drinker status were significantly associated with the incidence of pancreatic cancer (Fig. 2).

We conducted analyses by alternately using the T2DM-only, PAN-only, and T2DM-PAN groups as the reference. Among the four groups, both PPDM and T2DM-PAN demonstrated a significantly elevated risk of developing pancreatic cancer compared to the PAN-only or T2DM-only groups (Table 2). However, in direct comparisons, no significant difference was observed between the PPDM and T2DM-PAN groups (AOR, 0.95; 95% CI, 0.81 to 1.12) (Table 2).

Pancreatic cancer risk in DM subgroups based on insulin use

Additional analysis of the PPDM, T2DM-PAN, and T2DM-only groups by insulin use showed that in all cases, the risk of pancreatic cancer tended to be higher in patients with diabetes using insulin continuously than in those not using insulin in all the subgroups. Specifically, compared to the NDNP group, the PPDM group, which included individuals who had used insulin, exhibited a 17-fold increase in pancreatic cancer risk (AOR, 16.72; 95% CI, 9.50 to 29.43), whereas, the T2DM-PAN group, which included individuals who had used insulin, demonstrated a 8-fold increase (AOR, 7.78; 95% CI, 5.73 to 10.58) (Table 3). When the threshold for defining continuous insulin use was adjusted from at least five prescriptions within 3 years before the index date to three or two prescriptions, the odds ratio for pancreatic cancer in the continuous insulin user group exhibited a modest decrease. Nevertheless, the risk of pancreatic cancer remained significantly elevated among continuous insulin user groups within PPDM, T2DM-PAN, and T2DM-only, highlighting a consistent trend across these subgroups (Supplementary Tables 4 and 5).

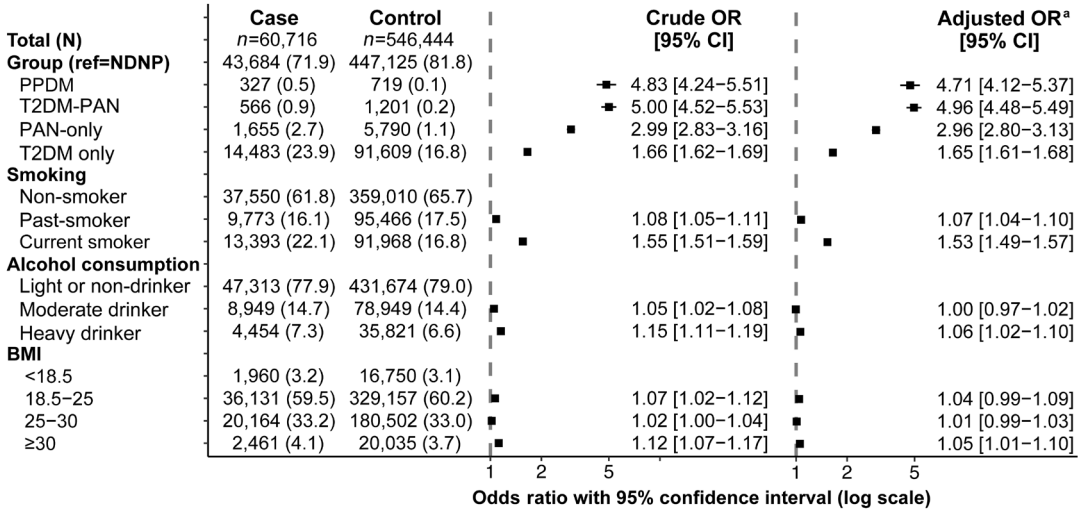

Fig. 2. Crude odds ratio (OR) (95% confidence interval [CI]) and adjusted ORs for the association between pancreatic cancer and categorized disease groups. NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only; BMI, body mass index. [a]Adjusted for smoking history, alcohol consumption, and BMI.

Table 2. Multivariable logistic regression with reference replaced with T2DM-only, PAN-only, and T2DM-PAN groups

Group	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
T2DM-only (ref)	14,483 (23.9)	91,609 (16.8)				
PPDM	327 (0.5)	719 (0.1)	2.92 (2.56–3.33)	<0.001	2.86 (2.50–3.26)	<0.001
T2DM-PAN	566 (0.9)	1,201 (0.2)	3.02 (2.73–3.34)	<0.001	3.01 (2.72–3.33)	<0.001
PAN-only	1,655 (2.7)	5,790 (1.1)	1.80 (1.70–1.91)	<0.001	1.80 (1.70–1.91)	<0.001
PAN-only (ref)	1,655 (2.7)	5,790 (1.1)				
PPDM	327 (0.5)	719 (0.1)	1.62 (1.40–1.86)	<0.001	1.59 (1.38–1.83)	<0.001
T2DM-PAN	566 (0.9)	1,201 (0.2)	1.67 (1.49–1.88)	<0.001	1.67 (1.49–1.88)	<0.001
T2DM-PAN (ref)	566 (0.9)	1,201 (0.2)				
PPDM	327 (0.5)	719 (0.1)	0.97 (0.82–1.14)	0.684	0.95 (0.81–1.12)	0.537

Values are presented as number (%).
T2DM-only, type 2 diabetes mellitus only; PAN-only, pancreatitis-only; OR, odds ratio; CI, confidence interval; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Analysis by duration of DM or pancreatitis

We subdivided the PPDM and T2DM-only groups according to the duration of diabetes and found that the shorter the duration of diabetes, the higher the risk of pancreatic cancer. In the T2DM-only group, new-onset T2DM (DM duration <365 days) was associated with a higher risk of pancreatic cancer than long-standing T2DM (DM duration >1,825 days) (AOR 9.10; 95% CI, 8.74 to 9.48 vs. AOR, 1.71; 95% CI, 1.66 to 1.76) (Table 4). Additionally, the PPDM group, with a diabetes duration of 3 years or less, had a more than 8-fold increased risk of pancreatic cancer compared to the NDNP group (Table 4). We conducted further analysis using PPDM or T2DM-only patients with a longer history of diabetes (DM duration >1,825 days) as the reference group and found that PPDM and T2DM-only patients with a shorter history of diabetes (duration less than 3 years) had a significantly higher association with pancreatic cancer risk (Supplementary Table 6). T2DM-PAN and PAN-only groups were further subdivided according to pan-

Table 3. Crude ORs (95% CI) and adjusted OR for the association between pancreatic cancer and disease groups further categorized by insulin use

Group	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP	43,685 (71.9)	447,125 (73.64)	Ref		Ref	
PPDM						
Insulin use (–)	183 (0.03)	471 (0.08)	4.14 (3.48–4.91)	<0.001	4.07 (3.42–4.83)	<0.001
Continuousinsulin users	34 (0.01)	19 (0)	18.28 (10.42–32.07)	<0.001	16.72 (9.50–29.43)	<0.001
Temporary insulin users	110 (0.02)	229 (0.04)	5.13 (4.08–6.45)	<0.001	4.97 (3.95–6.25)	<0.001
T2DM-PAN						
Insulin use (–)	160 (0.03)	412 (0.07)	4.09 (3.41–4.92)	<0.001	4.03 (3.35–4.84)	<0.001
Continuousinsulin users	72 (0.01)	97 (0.02)	7.92 (5.83–10.75)	<0.001	7.78 (5.73–10.58)	<0.001
Temporary insulin users	334 (0.06)	692 (0.11)	5.13 (4.50–5.85)	<0.001	5.12 (4.49–5.84)	<0.001
T2DM-only						
Insulin use (–)	9,608 (1.58)	63,455 (10.45)	1.58 (1.54–1.62)	<0.001	1.57 (1.54–1.61)	<0.001
Continuousinsulin users	875 (0.14)	3,235 (0.53)	2.83 (2.62–3.05)	<0.001	2.82 (2.62–3.04)	<0.001
Temporary insulin users	4,000 (0.66)	24,919 (4.1)	1.70 (1.64–1.76)	<0.001	1.69 (1.63–1.75)	<0.001
PAN-only	1,655 (0.27)	5,790 (0.95)	2.99 (2.83–3.16)	<0.001	2.97 (2.80–3.14)	<0.001

Values are presented as number (%).
OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; T2DM-only, type 2 diabetes mellitus only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Table 4. Association between pancreatic cancer risk and disease groups further categorized by DM duration without lag period

Variable	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP	424,729 (84.84)	35,766 (64.3)	Ref		Ref	
PPDM						
DM duration <365 days	104 (0.02)	231 (0.42)	26.61 (21.06–33.62)	<0.001	26.54 (20.99–33.56)	0.001
DM duration 365–729 days	84 (0.02)	67 (0.12)	9.94 (7.18–13.75)	0.001	9.79 (7.07–13.57)	0.001
DM duration 730–1,094 days	65 (0.01)	44 (0.08)	9.05 (6.14–13.34)	0.001	8.83 (5.99–13.01)	0.001
DM duration 1,095–1,825 days	127 (0.03)	57 (0.1)	5.60 (4.08–7.69)	0.001	5.43 (3.95–7.46)	0.001
DM duration >1,825 days	235 (0.05)	84 (0.15)	4.59 (3.57–5.91)	0.001	4.51 (3.50–5.81)	0.001
T2DM-only						
DM duration <365 days	6,199 (1.24)	4,672 (8.4)	9.10 (8.74–9.47)	0.001	9.10 (8.74–9.48)	0.001
DM duration 365–729 days	6,192 (1.24)	1,523 (2.74)	2.96 (2.79–3.13)	0.001	2.97 (2.80–3.14)	0.001
DM duration 730–1,094 days	6,207 (1.24)	1,094 (1.97)	2.14 (2.00–2.28)	0.001	2.15 (2.01–2.29)	0.001
DM duration 1,095–1,825 days	11,613 (2.32)	1,680 (3.02)	1.75 (1.66–1.84)	0.001	1.76 (1.67–1.85)	0.001
DM duration >1,825 days	38,672 (7.72)	5,312 (9.55)	1.71 (1.65–1.76)	0.001	1.71 (1.66–1.76)	0.001

Values are presented as number (%). Analysis was conducted without applying a lag period to include newly developed diabetes mellitus cases within 1 year of pancreatic cancer diagnosis.
DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-only, type 2 diabetes mellitus only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

creatitis duration, and new-onset pancreatitis was associated with a higher risk of pancreatic cancer in both groups (Supplementary Table 7).

Sensitivity analysis

The risk of pancreatic cancer was relatively higher in the PPDM, T2DM-PAN, PAN-only, and T2DM-only groups when the lag period was shorter than 1 year (no lag period or 180-day lag period) compared to when the lag period was longer than 1 year (lag periods of 1, 2, 3, or 5 years). Whereas, the PPDM, T2DM-PAN, PAN-only, and T2DM-only groups maintained high ORs for pancreatic cancer when the lag period was increased to more than 1 year (Supplementary Table 8).

To further validate our findings, we conducted a sensitivity analysis by excluding individuals who had undergone pancreatectomy prior to the index date (311 individuals in the cancer group and 96 in the control group). The results of this analysis were consistent with those identified when pancreatectomy cases were included, indicating that the exclusion of these individuals did not significantly alter the observed associations (Supplementary Table 9).

DISCUSSION

The main finding of our study was that the coexistence of diabetes and pancreatitis (PPDM and T2DM-PAN groups) increased the risk of pancreatic cancer more than the existence of T2DM-only or PAN-only did. In this study, compared to the NDNP group, both the T2DM-only and PAN-only groups showed a significantly increased risk of pancreatic cancer. Additionally, both the T2DM-PAN and PPDM groups had a significantly higher risk of pancreatic cancer than did the T2DM-only or PAN-only groups. These results suggest that T2DM and pancreatitis independently serve as risk factors for pancreatic cancer, regardless of the order in which they occur, and that the concurrent presence of both diseases is associated with a higher risk of pancreatic cancer compared to having only one of the diseases.

Considering that pancreatic cancer screening is recommended for high-risk populations, defined as individuals with a 5-fold increased relative risk [14], we further analyzed the PPDM, T2DM-PAN, and T2DM-only groups with respect to insulin usage and duration of diabetes to pinpoint subgroups that were associated with more than a 5-fold increase in pancreatic cancer risk compared to the general population. Firstly, we found that insulin usage before the index date was associated with a significantly higher risk of pancreatic cancer compared to lack of insulin usage. PPDM, when accompanied by continuous insulin usage, presented a 17-fold increased risk of pancreatic cancer, and T2DM-PAN with continuous insulin use demonstrated a 8-fold increased risk. The reason behind this finding could be that the use of insulin indicates difficulty in controlling blood sugar, which may reflect hyperglycemia caused by β-cell failure in the progression of diabetes [30,31] or reverse causality of pancreatic cancer [32]. Particularly, PPDM with continuous insulin use was associated with an approximately 17-fold increased risk of pancreatic cancer compared with NDNP (AOR, 9.84; 95% CI, 6.77 to 14.29), suggesting the need for careful surveillance for pancreatic cancer in patients with PPDM on insulin. Secondly, we found that the PPDM group with new-onset diabetes exhibited significantly stronger associations with pancreatic cancer than did the NDNP group. The T2DM-only group had a 9-fold increased risk of pancreatic cancer compared to the NDNP group up to only 1 year after diabetes onset and about 2-fold thereafter, while the PPDM group was associated with over 8-fold increased risk of pancreatic cancer compared to that of NDNP for a duration of up to 3 years after diabetes onset. These findings are consistent with previously published research, which reported that individuals with new-onset diabetes have a substantially higher risk of developing pancreatic cancer compared to those with long-standing diabetes. The concordance of our results with previous research highlights the critical need to consider the temporal relationship between diabetes onset and pancreatic cancer risk in clinical practice [33]. Furthermore, as supported by Sharma et al. [24], hyperglycemia and new-onset diabetes may precede pancreatic ductal adenocarcinoma diagnosis by several years, suggesting diabetes might serve as an early marker of pancreatic cancer.

Although the evidence presented previously is limited to acute pancreatitis, diabetes that develops after pancreatitis is likely multifactorial, with a variety of potential contributing factors in individual patients, including (1) loss of islet cell mass due to acute pancreatitis; (2) autoimmunity due to acute pancreatitis; (3) common risk factors for acute pancreatitis and diabetes; (4) local and systemic inflammatory responses; and (5) alterations in the insulin-incretin axis, or a combination of these factors [34]. Furthermore, a previous systemic meta-analysis showed that severe acute pancreatitis was associated with increased incidence of DM [35]. Although our study was not

limited to acute pancreatitis, this suggests that new-onset diabetes after pancreatitis may have been associated with a higher risk of pancreatic cancer because new-onset diabetes after pancreatitis is itself a reflection of the severity of the pancreatitis.

In this study, no significant differences were observed when directly comparing the T2DM-PAN and PPDM groups (AOR, 0.95; 95% CI, 0.81 to 1.12), and the T2DM-PAN group had a significantly higher risk of pancreatic cancer than did the PAN-only group (AOR, 1.67; 95% CI, 1.49 to 1.88). The order of each disease's onset did not significantly contribute to the risk of pancreatic cancer in patients with coexisting diabetes and pancreatitis. Importantly, our main finding demonstrated that the coexistence of these two conditions substantially elevated the risk of pancreatic cancer. However, these results were inconsistent with those of a previous study in which the PAN-only and T2DM-PAN groups had similar risks of pancreatic cancer, and the PPDM group had a significantly higher pancreatic cancer risk than did the T2DM-PAN group [17]. This discrepancy may be ascribed to two principal factors. Firstly, the variation in the study populations is noteworthy. The prior study utilized data from the New Zealand Cancer Registry (NZCR), wherein, the patients not developing pancreatic cancer were subsequently diagnosed with other cancers. Moreover, the NZCR study encompassed a comparatively older demographic than did our study, with the mean age at diagnosis being 68.9 years for PPDM. Furthermore, Asian patients accounted for less than 10% of the study population. The etiology of pancreatitis (e.g., alcohol and tobacco use) and clinical outcomes (such as morphologic abnormalities and endocrine insufficiency) may vary by ethnicity [36]. Therefore, it can be hypothesized that the progression from pancreatitis to pancreatic cancer may also vary between different ethnic groups. Moreover, the incidence of pancreatic cancer also differs according to ethnicity and geographic location, likely due to differences in lifestyle, living standards, socioeconomic factors, and genetic predispositions [37]. Thus, the differences observed between our study and the New Zealand study could be attributed to interethnic variations in the development and progression of pancreatitis, as well as in the incidence of pancreatic cancer. Secondly, the distinction in study design played a significant role. T2DM-PAN and PPDM were delineated based on the sequence of disease onset, signifying an immortal time between the diagnosis of each condition. To circumvent the issue of immortal time bias in disease classification, we used a nested case-control design [38].

In our study, the lag period of the main outcome was set to 1 year to eliminate reverse causality, and the lag period was also set to 0, 0.5, 2, 3, and 5 years in the sensitivity analysis. Because high blood glucose can be a symptom of pancreatic cancer, consideration of reverse causality is necessary when evaluating diabetes as a risk factor in pancreatic cancer research. Notably, 74% to 88% of patients are diagnosed with diabetes within 24 months following their diagnosis of pancreatic ductal adenocarcinoma [39]. High serum glucose level may be one of the symptoms of pancreatic cancer, and the following explanatory mechanisms have been proposed: (1) diabetogenic factors secreted by the pancreatic tumor may reduce insulin secretion and sensitivity [40] and (2) β-cell dedifferentiation by pancreatic cancer may cause dysfunction of β-cells, leading to hyperglycemia [41]. Further, it is not known how many years it takes for symptoms to appear after the development of pancreatic cancer [42,43]. Hence, when diabetes is diagnosed before pancreatic cancer, it is difficult to determine exactly whether diabetes is a cause or a symptom of pancreatic cancer. In previous studies which have analyzed the relationship between diabetes or pancreatitis and pancreatic cancer, various lag periods were applied to exclude reverse causality [5,44]. In the sensitivity analysis of this study, the T2DM-only, PAN-only, T2DM-PAN, and PPDM groups exhibited a significantly increased risk of pancreatic cancer compared to the NDNP group at all lag periods. Importantly, the highest OR was observed in analyses conducted without a lag period conditions. However, even in sensitivity analyses with a lag period longer than 1 year, all groups were associated with an increased risk of pancreatic cancer compared to that of the NDNP group, suggesting that diabetes and pancreatitis not only have a reverse causality with pancreatic cancer but are also risk factors for pancreatic cancer.

A key strengths of this study is the higher number of pancreatic cancer cases compared to that of other studies, attributed to data derived from a comprehensive registry of the entire Korean population, a significant aspect considering the rarity of this disease. Furthermore, initiation of a special reimbursement program in September 2005 by the Korean NHIS, aimed at reducing the medical costs for patients with cancer, enhanced the study's validity. As outlined in the methods section, patients were required to meet specific diagnostic criteria to qualify for special medical expense coverage. These stringent criteria ensured that the accuracy of pancreatic cancer diagnoses remained high, even when relying solely on insurance claims data. Additionally, utilizing the NDNP group as a reference en-

abled the evaluation of pancreatic cancer risk in the T2DM-only, PAN-only, T2DM-PAN, and PPDM groups compared to that of the general population. Importantly, the collection of data from medical examinations provided valuable insights into factors like smoking history, alcohol consumption, and BMI.

This study has some limitations that warrant discussion. Firstly, the histological type and stage of pancreatic cancer were not included in the NHID; therefore, these data could not be considered in our study. Secondly, discrepancies between medical diagnoses and diagnoses using operational definitions in claims data may have reduced the accuracy of the analysis. Therefore, we tried to improve the accuracy of the operational definitions of disease by using information such as hospitalization status, number of outpatient visits, medication use, and special reimbursement codes to define diseases [45]. Thirdly, our study lacks data on glycosylated hemoglobin (HbA1c) levels, which restricts our ability to assess the severity of diabetes and its potential impact on the development of pancreatic cancer. Future studies should incorporate HbA1c measurements to better evaluate this relationship. Lastly, due to the characteristics of the NHIS-NHID dataset, data prior to 2002 were unavailable, and therefore only patients who were newly diagnosed with diabetes from 2003 thereafter, for whom the duration of diabetes could be clearly established, were included in the analysis. Consequently, individuals with a diabetes duration greater than 20 years were excluded from this study. It is possible that if patients with longer diabetes durations had been included, they might have demonstrated a higher risk compared to those with newly onset diabetes; however, this could not be assessed due to the limitations of the dataset.

In conclusion, we demonstrated that the T2DM-PAN and PPDM groups had a higher risk of pancreatic cancer than did the T2DM-only and PAN-only groups. Importantly, even within the PPDM groups, a diagnosis of diabetes within 3 years or insulin use was associated with a significantly increased risk of pancreatic cancer, suggesting the need for aggressive pancreatic cancer screening for these patients. Because PPDM accounts for the second highest proportion of diabetes after T2DM [46], close follow-up is needed for the high-risk subgroup of patients with PPDM for pancreatic cancer development.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0277.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: all authors.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: Y.K., E.S.K.
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Supplementary Table 1. Baseline demographics and clinical characteristics according to cancer status for five groups subdivided by diabetes and pancreatitis diagnoses

Variable	Control observations				
	NDNP (*n*=447,125)	PPDM (*n*=719)	T2DM-PAN (*n*=1,201)	PAN-only (*n*=5,790)	T2DM-only (*n*=91,609)
Age at index date, yr	68±11	73±9	75±9	73±10	72±9
<40	2,996 (0.7)	0	1 (0.1)	11 (0.2)	25 (0)
40–<50	25,367 (5.7)	5 (0.7)	4 (0.3)	119 (2.1)	1,010 (1.1)
50–<60	76,959 (17.2)	63 (8.8)	64 (5.3)	549 (9.5)	7,991 (8.7)
60–<70	127,563 (28.5)	166 (23.1)	240 (20.0)	1,309 (22.6)	24,334 (26.6)
70–<80	140,177 (31.4)	305 (42.4)	464 (38.6)	2,102 (36.3)	37,384 (40.8)
≥80	74,063 (16.6)	180 (25)	428 (35.6)	1,700 (29.4)	20,865 (22.8)
Sex					
Male	241,921 (54.1)	457 (63.6)	714 (59.5)	3,386 (58.5)	51,287 (56.0)
Female	205,204 (45.9)	262 (36.4)	487 (40.5)	2,404 (41.5)	40,322 (44.0)
Smoking					
Non-smoker	294,707 (65.9)	421 (58.6)	792 (65.9)	3,652 (63.1)	59,438 (64.9)
Past-smoker	76,190 (17)	143 (19.9)	234 (19.5)	1,188 (20.5)	17,711 (19.3)
Current smoker	76,228 (17)	155 (21.6)	175 (14.6)	950 (16.4)	14,460 (15.8)
Alcohol consumption					
Light or non-drinker	351,540 (78.6)	572 (79.6)	982 (81.8)	4,617 (79.7)	73,963 (80.7)
Moderate drinker	65,998 (14.8)	77 (10.7)	128 (10.7)	737 (12.7)	12,009 (13.1)
Heavy drinker	29,587 (6.6)	70 (9.7)	91 (7.6)	436 (7.5)	5,637 (6.2)
BMI, kg/m^2	23.8±3.2	24±3.4	24.4±3.2	23.4±3.2	24.8±3.2
<18.5	14,817 (3.3)	38 (5.3)	37 (3.1)	319 (5.5)	1,539 (1.7)
18.5–<25	276,721 (61.9)	401 (55.8)	677 (56.4)	3,700 (63.9)	47,658 (52)
25–<30	141,422 (31.6)	250 (34.8)	428 (35.6)	1,608 (27.8)	36,794 (40.2)
≥30	14,165 (3.2)	30 (4.2)	59 (4.9)	163 (2.8)	5,618 (6.1)
Household income					
Missing	7,522 (1.7)	9 (1.3)	19 (1.6)	91 (1.6)	1,511 (1.6)
Low	55,798 (12.5)	96 (13.4)	148 (12.3)	763 (13.2)	11,824 (12.9)
Mid-low	62,524 (14.0)	105 (14.6)	175 (14.6)	817 (14.1)	12,598 (13.8)
Middle	93,657 (20.9)	173 (24.2)	247 (20.6)	1,269 (21.9)	18,825 (20.5)
Mid-high	96,169 (21.5)	161 (22.4)	246 (20.5)	1,227 (21.2)	19,467 (21.3)
High	131,455 (29.4)	175 (24.3)	366 (30.5)	1,623 (28.0)	27,384 (29.9)
CCI					
0	383,341 (85.7)	362 (50.3)	443 (36.9)	3,506 (60.6)	60,088 (65.6)
1	33,345 (7.5)	81 (11.3)	213 (17.7)	898 (15.5)	11,662 (12.7)
2	15,072 (3.4)	93 (12.9)	176 (14.7)	593 (10.2)	7,780 (8.5)
≥3	15,367 (3.4)	183 (25.5)	369 (30.7)	793 (13.7)	12,079 (13.2)

Values are presented as mean±standard deviation or number (%). Statistical comparisons were performed using the *t*-test for continuous variables, and the chi-square test for categorical variables.
NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only; BMI, body mass index; CCI, Charlson comorbidity index.

Supplementary Table 2. Baseline demographics and clinical characteristics according to cancer status for five groups subdivided by diabetes and pancreatitis diagnoses

Variable	Pancreatic cancer cases				
	NDNP (*n*=43,685)	PPDM (*n*=327)	T2DM-PAN (*n*=566)	PAN-only (*n*=1,655)	T2DM-only (*n*=14,483)
Age at index date, yr	68±12	69±11	72±10	69±12	71±9
<40	315 (0.7)	0	0	11 (0.7)	11 (0.1)
40–<50	2,610 (6.0)	16 (4.9)	13 (2.3)	96 (5.8)	210 (1.4)
50–<60	7,705 (17.6)	51 (15.6)	55 (9.7)	255 (15.4)	1,448 (10.0)
60–<70	12,291 (28.1)	88 (26.9)	159 (27.6)	447 (27.0)	4,086 (28.2)
70–<80	13,434 (30.8)	114 (24.9)	198 (35.0)	510 (30.8)	5,792 (40.0)
≥80	7,330 (16.8)	58 (17.7)	144 (25.4)	336 (20.3)	2,936 (20.3)
Sex					
Male	23,500 (53.8)	230 (70.3)	367 (64.8)	1,035 (62.5)	7,953 (54.9)
Female	20,185 (46.2)	97 (29.7)	199 (35.2)	620 (37.5)	6,530 (45.1)
Smoking					
Non-smoker	27,258 (62.4)	149 (45.6)	305 (53.9)	921 (55.6)	8,917 (61.6)
Past-smoker	6,742 (15.4)	73 (22.3)	113 (20)	308 (18.6)	2,537 (17.5)
Current smoker	9,685 (22.2)	105 (32.1)	148 (26.1)	426 (25.7)	3,029 (20.9)
Alcohol consumption					
Light or non-drinker	33,836 (77.5)	242 (74)	442 (78.1)	1,240 (74.9)	11,553 (79.8)
Moderate drinker	6,652 (15.2)	45 (13.8)	79 (14)	247 (14.9)	1,926 (13.3)
Heavy drinker	3,197 (7.3)	40 (12.2)	45 (8)	168 (10.2)	1,004 (6.9)
BMI, kg/m^2	24±3.2	23.6±4	23.8±3.4	23.2±3.2	24.8±3.2
<18.5	1,509 (3.5)	30 (9.2)	27 (4.8)	108 (6.5)	286 (2)
18.5–<25	26,770 (61.3)	193 (59)	341 (60.2)	1,053 (63.6)	7,774 (53.7)
25–<30	13,914 (31.9)	87 (26.6)	173 (30.6)	453 (27.4)	5,537 (38.2)
≥30	1,492 (3.4)	17 (5.2)	25 (4.4)	41 (2.5)	886 (6.1)
Household income					
Missing	669 (1.5)	9 (2.8)	8 (1.4)	32 (1.9)	258 (1.8)
Low	5,592 (12.9)	39 (11.9)	70 (12.4)	215 (13.0)	1,819 (12.6)
Mid-low	6,077 (13.9)	48 (14.7)	91 (16.1)	229 (13.8)	2,036 (14.1)
Middle	9,203 (21.1)	81 (24.8)	105 (18.6)	373 (22.5)	2,964 (20.5)
Mid-high	9,373 (21.5)	83 (25.4)	126 (22.3)	343 (20.7)	2,960 (20.4)
High	12,771 (29.2)	67 (20.5)	166 (29.3)	463 (28.0)	4,446 (30.7)
CCI					
0	36,958 (84.6)	147 (45)	158 (27.9)	923 (55.8)	9,386 (64.8)
1	3,468 (7.9)	50 (15.3)	123 (21.7)	301 (18.2)	1,888 (13)
2	1,613 (3.7)	44 (13.5)	89 (15.7)	175 (10.6)	1,307 (9)
≥3	1,646 (3.8)	86 (26.3)	196 (34.6)	256 (15.5)	1,902 (13.1)

Values are presented as mean±standard deviation or number (%). Statistical comparisons were performed using the *t*-test for continuous variables, and the chi-square test for categorical variables.
NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only; BMI, body mass index; CCI, Charlson comorbidity index.

Supplementary Table 3. Table of values from Fig. 2 with corresponding *P* values

Variable	Case (*n*=60,715)	Control (*n*=546,444)	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Group (ref=NDNP)	43,684 (71.9)	447,125 (81.8)	Ref		Ref	
PPDM	327 (0.5)	719 (0.1)	4.83 (4.24–5.51)	<0.001	4.71 (4.12–5.37)	<0.001
T2DM-PAN	566 (0.9)	1,201 (0.2)	5.00 (4.52–5.53)	<0.001	4.96 (4.48–5.49)	<0.001
PAN-only	1,655 (2.7)	5,790 (1.1)	2.99 (2.83–3.16)	<0.001	2.96 (2.80–3.13)	<0.001
T2DM-only	14,483 (23.9)	91,609 (16.8)	1.66 (1.62–1.69)	<0.001	1.65 (1.61–1.68)	<0.001
Smoking						
Non-smoker	37,550 (61.8)	359,010 (65.7)				
Past-smoker	9,773 (16.1)	95,466 (17.5)	1.08 (1.05–1.11)	<0.001	1.07 (1.04–1.10)	<0.001
Current smoker	13,393 (22.1)	91,958 (16.8)	1.55 (1.51–1.59)	<0.001	1.53 (1.49–1.57)	<0.001
Alcohol consumption						
Light or non-drinker	47,313 (77.9)	431,674 (79.0)				
Moderate drinker	8,949 (14.7)	78,949 (14.4)	1.05 (1.02–1.08)	<0.001	1.00 (0.97–1.02)	0.821
Heavy drinker	4,454 (7.3)	35,821 (6.6)	1.15 (1.11–1.19)	<0.001	1.06 (1.02–1.10)	0.001
BMI, kg/m^2						
<18.5	1,960 (3.2)	16,750 (3.1)				
18.5–<25	36,131 (59.5)	329,157 (60.2)	1.07 (1.02–1.12)	0.010	1.04 (0.99–1.09)	0.131
25–<30	20,164 (33.2)	180,502 (33.0)	1.02 (1.00–1.04)	0.056	1.01 (0.99–1.03)	0.364
≥30	2,461 (4.1)	20,035 (3.7)	1.12 (1.07–1.17)	<0.001	1.05 (1.01–1.10)	0.013

Values are presented as number (%).
NDNP, no diabetes and no pancreatitis; OR, odds ratio; CI, confidence interval; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only; BMI, body mass index.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 4. Crude ORs (95% CI) and adjusted OR for the association between pancreatic cancer and disease groups further categorized by insulin use (with continuous insulin use defined as at least three prescriptions within 3 years prior to the index date)

Group	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP	43,685 (71.9)	447,125 (73.64)	Ref		Ref	
PPDM						
Insulin use (–)	183 (0.03)	471 (0.08)	4.14 (3.48–4.91)	<0.001	4.07 (3.42–4.83)	<0.001
Continuous insulin users	45 (0.01)	32 (0.01)	14.67 (9.31–23.10)	<0.001	13.51 (8.55–21.34)	<0.001
Temporary insulin users	99 (0.02)	216 (0.04)	4.89 (3.85–6.21)	<0.001	4.75 (3.74–6.04)	<0.001
T2DM-PAN						
Insulin use (–)	160 (0.03)	412 (0.07)	4.09 (3.41–4.91)	<0.001	4.03 (3.35–4.84)	<0.001
Continuous insulin users	113 (0.02)	139 (0.02)	8.58 (6.69–11.01)	<0.001	8.54 (6.65–10.96)	<0.001
Temporary insulin users	293 (0.05)	650 (0.11)	4.80 (4.18–5.52)	<0.001	4.78 (4.16–5.49)	<0.001
T2DM-only						
Insulin use (–)	9,608 (1.58)	63,455 (10.45)	1.58 (1.54–1.62)	<0.001	1.57 (1.54–1.61)	<0.001
Continuous insulin users	1,091 (0.18)	4,143 (0.68)	2.75 (2.57–2.95)	<0.001	2.75 (2.57–2.94)	<0.001
Temporary insulin users	3,784 (0.62)	24,011 (3.95)	1.67 (1.61–1.73)	<0.001	1.66 (1.60–1.72)	<0.001
PAN-only	1,655 (0.27)	5,790 (0.95)	2.99 (2.82–3.16)	<0.001	2.96 (2.80–3.13)	<0.001

Values are presented as number (%).
OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; T2DM-only, type 2 diabetes mellitus only; PAN-only, pancreatitis-only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 5. Crude ORs (95% CI) and adjusted OR for the association between pancreatic cancer and disease groups further categorized by insulin use (with continuous insulin use defined as at least two prescriptions within 3 years prior to the index date)

Group	Case	Control	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP	43,685 (71.9)	447,125 (73.64)	Ref		Ref	
PPDM						
Insulin use (–)	183 (0.03)	471 (0.08)	4.14 (3.49–4.92)	<0.001	4.07 (3.43–4.84)	<0.001
Continuous insulin users	62 (0.01)	53 (0.01)	12.24 (8.48–17.67)	<0.001	11.63 (8.04–16.84)	<0.001
Temporary insulin users	82 (0.01)	195 (0.03)	4.48 (3.46–5.81)	<0.001	4.33 (3.34–5.62)	<0.001
T2DM-PAN						
Insulin use (–)	160 (0.03)	412 (0.07)	4.09 (3.41–4.92)	<0.001	4.03 (3.35–4.84)	<0.001
Continuous insulin users	161 (0.03)	201 (0.03)	8.46 (6.87–10.41)	<0.001	8.38 (6.80–10.32)	<0.001
Temporary insulin users	245 (0.04)	588 (0.1)	4.44 (3.82–5.16)	<0.001	4.43 (3.81–5.15)	<0.001
T2DM-only						
Insulin use (–)	9,608 (1.58)	63,455 (10.45)	1.58 (1.54–1.62)	<0.001	1.57 (1.54–1.61)	<0.001
Continuous insulin users	1,414 (0.23)	5,816 (0.96)	2.55 (2.40–2.70)	<0.001	2.54 (2.40–2.70)	<0.001
Temporary insulin users	3,461 (0.57)	22,338 (3.68)	1.64 (1.58–1.7)	<0.001	1.63 (1.57–1.69)	<0.001
PAN-only	1,655 (0.27)	5,790 (0.95)	2.99 (2.82–3.16)	<0.001	2.96 (2.80–3.13)	<0.001

Values are presented as number (%).
OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; T2DM-only, type 2 diabetes mellitus only; PAN-only, pancreatitis-only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 6. Association between pancreatic cancer risk and disease groups stratified by pancreatitis duration, with the reference group defined as patients with DM duration >1,825 days

Variable	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
PPDM (ref. PPDM patients with DM duration >1,825 days)				
DM duration <365 days	5.80 (4.11–8.17)	<0.001	5.88 (4.17–8.31)	<0.001
DM duration 365–729 days	2.16 (1.43–3.26)	<0.001	2.17 (1.44–3.28)	<0.001
DM duration 730–1,094 days	1.97 (1.24–3.13)	0.004	1.96 (1.23–3.11)	0.004
DM duration 1,095–1,825 days	1.22 (0.81–1.83)	0.334	1.20 (0.80–1.81)	0.369
T2DM-only (ref. T2DM-only patients with DM duration >1,825 days)				
DM duration <365 days	5.33 (5.08–5.60)	<0.001	5.33 (5.08–5.59)	<0.001
DM duration 365–729 days	1.73 (1.63–1.85)	<0.001	1.74 (1.63–1.85)	<0.001
DM duration 730–1,094 days	1.25 (1.17–1.35)	<0.001	1.26 (1.17–1.35)	<0.001
DM duration 1,095–1,825 days	1.02 (0.97–1.09)	0.423	1.03 (0.97–1.09)	0.346

Analysis was conducted without applying a lag period to include newly developed diabetes mellitus cases within 1 year of pancreatic cancer diagnosis.
DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; PPDM, post-pancreatitis diabetes mellitus; T2DM-only, type 2 diabetes mellitus only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 7. Association between pancreatic cancer risk and disease groups further categorized by pancreatitis duration

Variable	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP	Ref		Ref	
T2DM-PAN				
PAN duration <365 days	67.40 (56.15–80.91)	<0.001	66.68 (55.53–80.08)	<0.001
PAN duration 365–729 days	10.11 (7.81–13.09)	<0.001	9.83 (7.59–12.74)	<0.001
PAN duration 730–1,094 days	5.48 (4.00–7.51)	<0.001	5.45 (3.97–7.47)	<0.001
PAN duration 1,095–1,824 days	5.50 (4.23–7.14)	<0.001	5.49 (4.22–7.13)	<0.001
PAN duration >1,825 days	4.01 (3.19–5.05)	<0.001	3.97 (3.16–5.00)	<0.001
PAN-only				
PAN duration <365 days	52.39 (47.81–57.41)	<0.001	51.67 (47.15–56.63)	<0.001
PAN duration 365–729 days	5.92 (5.13–6.84)	<0.001	5.85 (5.06–6.76)	<0.001
PAN duration 730–1,094 days	4.04 (3.42–4.76)	<0.001	3.99 (3.38–4.71)	<0.001
PAN duration 1,095–1,824 days	3.65 (3.19–4.17)	<0.001	3.60 (3.15–4.12)	<0.001
PAN duration >1,825 days	2.44 (2.23–2.68)	<0.001	2.42 (2.21–2.66)	<0.001

OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN, pancreatitis; PAN-only, pancreatitis-only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 8. Association between pancreatic cancer risk and disease groups according to lag period

Variable	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP (no lag period) (ref)				
PPDM	9.17 (8.23–10.22)	<0.001	9.03 (8.10–10.06)	<0.001
T2DM-PAN	13.88 (12.91–14.93)	<0.001	13.77 (12.80–14.81)	<0.001
PAN-only	8.37 (8.02–8.72)	<0.001	8.26 (7.92–8.61)	<0.001
T2DM-only	2.36 (2.31–2.40)	<0.001	2.36 (2.31–2.41)	<0.001
NDNP (lag period: 180 days) (ref)				
PPDM	6.03 (5.33–6.82)	<0.001	5.92 (5.23–6.70)	<0.001
T2DM-PAN	5.71 (5.20–6.28)	<0.001	5.66 (5.15–6.22)	<0.001
PAN-only	3.33 (3.16–3.52)	<0.001	3.31 (3.14–3.49)	<0.001
T2DM only	1.81 (1.78–1.85)	<0.001	1.81 (1.77–1.85)	<0.001
NDNP (lag period: 1 year) (ref)				
PPDM	4.83 (4.24–5.51)	<0.001	4.71 (4.12–5.37)	<0.001
T2DM-PAN	5.00 (4.52–5.53)	<0.001	4.96 (4.48–5.49)	<0.001
PAN-only	2.99 (2.83–3.16)	<0.001	2.96 (2.80–3.13)	<0.001
T2DM only	1.66 (1.62–1.69)	<0.001	1.65 (1.61–1.68)	<0.001
NDNP (lag period: 2 years) (ref)				
PPDM	4.25 (3.66–4.94)	<0.001	4.17 (3.59–4.84)	<0.001
T2DM-PAN	4.29 (3.83–4.81)	<0.001	4.22 (3.76–4.73)	<0.001
PAN-only	2.65 (2.49–2.81)	<0.001	2.63 (2.48–2.79)	<0.001
T2DM only	1.55 (1.52–1.58)	<0.001	1.54 (1.51–1.58)	<0.001
NDNP (lag period: 3 years) (ref)				
PPDM	3.75 (3.18–4.43)	<0.001	3.65 (3.09–4.30)	<0.001
T2DM-PAN	4.06 (3.58–4.61)	<0.001	4.00 (3.53–4.54)	<0.001
PAN-only	2.51 (2.36–2.68)	<0.001	2.49 (2.34–2.66)	<0.001
T2DM only	1.52 (1.49–1.55)	<0.001	1.51 (1.48–1.55)	<0.001
NDNP (lag period: 5 years) (ref)				
PPDM	3.85 (3.14–4.73)	<0.001	3.77 (3.07–4.64)	<0.001
T2DM-PAN	3.20 (2.74–3.74)	<0.001	3.18 (2.72–3.71)	<0.001
PAN-only	2.39 (2.22–2.57)	<0.001	2.36 (2.20–2.54)	<0.001
T2DM only	1.50 (1.47–1.54)	<0.001	1.50 (1.46–1.53)	<0.001

OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.

Supplementary Table 9. Sensitivity analysis excluding patients with a history of pancreatectomy prior to baseline

Variable	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
NDNP (ref)				
PPDM	4.40 (3.84–5.05)	<0.001	4.28 (3.73–4.91)	<0.001
T2DM-PAN	4.77 (4.30–5.28)	<0.001	4.72 (4.26–5.24)	<0.001
PAN-only	2.84 (2.68–3.01)	<0.001	2.81 (2.66–2.98)	<0.001
T2DM-only	1.65 (1.61–1.68)	<0.001	1.64 (1.61–1.68)	<0.001
T2DM-PAN (ref)				
PPDM vs. T2DM-PAN	0.92 (0.78–1.09)	0.359	0.91 (0.76–1.08)	0.263

OR, odds ratio; CI, confidence interval; NDNP, no diabetes and no pancreatitis; PPDM, post-pancreatitis diabetes mellitus; T2DM-PAN, type 2 diabetes mellitus followed by pancreatitis; PAN-only, pancreatitis-only; T2DM-only, type 2 diabetes mellitus only.
[a]Adjusted for smoking history, alcohol consumption, and body mass index.