Effects of pancreatitis and type 2 diabetes on the development of pancreatic cancer: An analysis of the Korean National Health Information Database

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ABSTRACT

Effects of pancreatitis and type 2 diabetes on the development of pancreatic cancer: An analysis of the Korean National Health Information database

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Aim: Although pancreatic cancer has a high mortality rate, its incidence is low; hence, screening tests are not recommended for the general population but only for high-risk groups. Identifying high-risk individuals who would benefit from pancreatic cancer screening is an important challenge. This study aimed to determine the 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. The control group comprised patients who were newly diagnosed with pancreatic cancer from 2007 to 2021; these individuals were matched according to the time of follow-up, sex, and age at the index date. Patients were categorized into the following groups by index date: type 2 diabetes only (T2D only), pancreatitis only (PAN only), type 2 diabetes followed by pancreatitis (T2D-PAN), pancreatitis followed by diabetes mellitus (PPDM), and no diabetes and no pancreatitis (NDNP). Conditional logistic regression was used to determine the significant associations of each group with pancreatic cancer development risk.

Results: type 2 diabetes and pancreatitis were found to be an independent risk factor for pancreatitis, and their simultaneous presence was associated with a higher risk of pancreatic cancer. In conditional logistic regression analysis, the risk of pancreatic cancer were significantly higher in the T2D-only (adjusted odds ratio [AOR] 1.65; 95% confidence interval [CI] 1.61–1.68), PAN-only (AOR 2.96; 95% CI 2.80–3.13]), T2D-PAN(AOR 4.96; 95% CI 4.48–5.49]) and PPDM(AOR 4.71; 95% CI 4.12–5.37]) groups than in the NDNP group. Among these four groups, the T2D-PAN and PPDM groups were associated with a higher risk of pancreatic cancer than the T2D-only and PAN-only groups. However, there was no significant difference in the risk of pancreatic cancer between the T2D-PAN and PPDM groups (AOR, 0.95; 95% CI, 0.81–1.12). Among patients with diabetes, the use of insulin before the index date was associated with a higher risk of pancreatic cancer compared to those who did not use insulin.

Conclusion: The PPDM and T2D-PAN groups had a significantly higher risk of pancreatic cancer than the T2D-only and PAN-only groups and the general population without diabetes and pancreatitis. Furthermore, the PPDM and T2D-PAN groups that used insulin or had a short time interval between pancreatitis and DM had a significantly higher risk of pancreatic cancer than the NDNP group, suggesting that a more aggressive pancreatic cancer screening should be considered in these patients.

Key words: pancreatic cancer, diabetes mellitus, type 2 diabetes mellitus, pancreatitis, post-pancreatitis diabetes mellitus

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I. INTRODUCTION

1. Background

Pancreatic cancer ranked 12th in terms of incidence (495,773 new cases), but was the 7th leading cause of cancer mortality (466,003 deaths) worldwide in 2020.[1] In South Korea, pancreatic cancer was the 8th most commonly diagnosed cancer (8,414 new cases), with the 5th highest age-standardized cancer mortality rate (5.7 per 100,000) in 2020. [2] 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.[3] In most cases, pancreatic cancer is diagnosed at the distant stage (48.2%), while only some cases are diagnosed at the local stage (13.0%).[3] Data from South Korea have shown a similar trend to those from the United States. In South Korea, the 5-year relative survival rates of males with pancreatic cancer from 2016 to 2020 were 42.7%, 17.0%, and 1.9% at localized, regional, and distant stages, respectively.[2] One of the reasons why pancreatic cancer has one of the highest mortality rates is that it is mostly diagnosed

in advanced stages rather than in the early stages owing to a lack of effective screening strategies. In addition, as the incidence of pancreatic cancer continues to rise, {Klein, 2019 #235} there is a growing need for effective screening strategies for pancreatic cancer.

Pancreatitis, smoking, alcohol, obesity, diabetes and some specific genetic conditions are some of the known high-risk factors for pancreatic cancer.[4] A previous meta-analyses demonstrated that the risk of developing pancreatic cancer was 1.5- to 2.0-fold[5] higher in the type 2 diabetes group and 2.0-fold higher in the type 1 diabetes group than in the healthy control group.[6] Chronic pancreatitis is a well-known risk factor for pancreatic cancer,[7-9] and recent studies have reported that acute pancreatitis is also associated with pancreatic cancer.[10,11,12] Although diabetes mellitus (DM)[13-15] and pancreatitis[7-12] are known risk factors for pancreatic cancer, current guidelines do not recommend aggressive screening in patients with diabetes or pancreatitis pancreatic cancer screening is recommended for high-risk populations, including individuals with a >5% lifetime risk or fivefold increased relative risk, as suggested by the international Cancer of the Pancreas Screening (CAPS) consortium.[16] The current guidelines recommend further examination or changing follow-up intervals if patients at high risk for pancreatic cancer develop new-onset diabetes.[17]

Previous studies on the risk factors for pancreatic cancer have attempted to simultaneously analyze diabetes and pancreatitis. 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.[18,19] Another population-based cohort study in South Korea found that patients with diabetes and acute pancreatitis had a higher risk of pancreatic cancer than patients with type 2 diabetes alone.[20] In addition, a study based on the nationwide cancer registry in New Zealand did not analyze diabetes and pancreatitis as separate categories, but instead categorized them according to the order of the onset of pancreatitis and diabetes, such as pancreatitis after T2D and post-pancreatitis diabetes mellitus (PPDM, Type 3c diabetes mellitus secondary to pancreatitis), and reported that PPDM was associated with a significantly higher risk of pancreatic cancer than type 2 diabetes.[21] The results of previous studies suggest that it may be possible to

identify patients for whom screening for pancreatic cancer may be effective by identifying subgroups of patients with both diabetes and pancreatitis who have additional factors that may increase their risk of pancreatic cancer. However, one of the main limitations of the previous studies is the small number of pancreatic cancer cases. Additionally, studies in Taiwan and Korea did not consider the order of occurrence of diabetes and pancreatitis, and the New Zealand study had an immortality time bias in its disease definition. Although the results of the previous studies have important implications, more studies with larger numbers of patient with pancreatic cancer are needed to identify high-risk subgroups for pancreatic cancer screening.

2. Study objectives

This nationwide population-based study had three main objectives: (1) To analyze the combined effects of diabetes and pancreatitis on the risk of pancreatic cancer compared to the absence of both diabetes and pancreatitis; (2) to analyze whether there is a difference in the risk of pancreatic cancer based on the order of the onset of diabetes and pancreatitis; and (3) to specify subgroups at high risk for pancreatic cancer for whom screening may be recommended.

II. MATERIALS AND METHODS

1. Data Sources

The data used in the current study were extracted from the national health information data (NHID) of the Korean National Health Insurance Service (NHIS) for the period between 2002 and 2021.[22] The Korean NHID contains a nationwide claims database and health examination data.[23] The NHIS, as the single insurer, pays the costs based on the billing records of healthcare providers.[22] The NHIS covers almost the entire population of South Korea, spanning over 50 million as of 2020, and provides a platform for using customized retrospective cohort data.[24,25] The NHID contains information on income-based insurance contributions, demographic variables, and date of death as well as information on records of inpatient and outpatient usage (diagnosis codes, hospital admission, and special reimbursement codes) and medical treatment (prescriptions and procedures) from January 2002 to December 2021.[25] This study adhered to the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the Yonsei University College of Medicine (No. 4-2021-1489).

2. Study population

A. Case selection

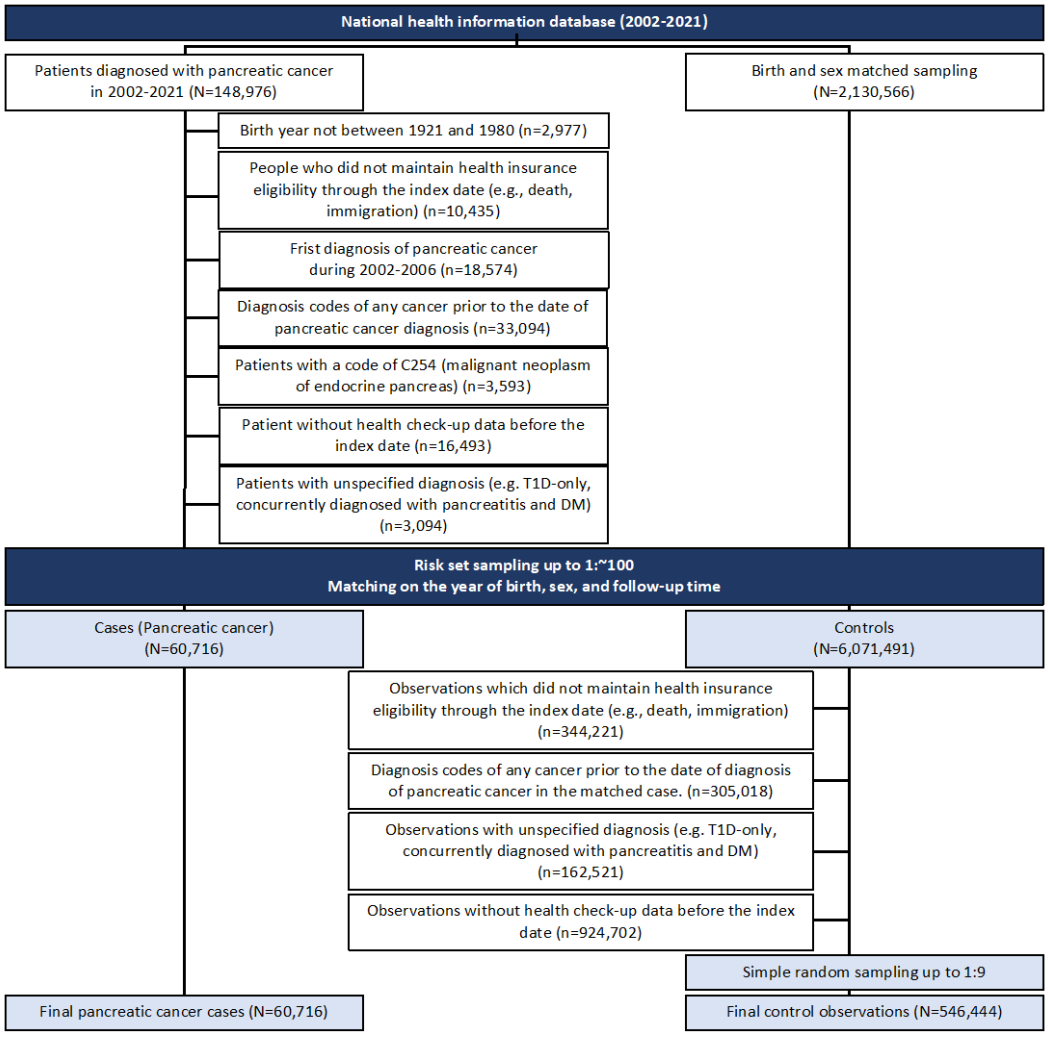
The data were collected from 2002 to 2021, but due to a 5-year washout period, we analyzed patients who were newly diagnosed with pancreatic cancer (ICD-10: C25 code and V193 code) from 2007 to 2021 as the case group and matched patients who did not develop pancreatic cancer as the control group. The NHID started using the International Classification of Disease-Tenth Revision-Clinical Modification (ICD-10-CM) and special reimbursement codes (V codes) since September 2005 to reduce the copayment rate to 5% for specific diseases such as cancers. In order to register a patient with cancer under the V193 code, the diagnosis must be confirmed by a required test (e.g., histologic, cytologic, biochemical, immunohistochemical, hematologic, imaging, or diagnostic surgery) based on

criteria established by the Ministry of Health and Welfare. Therefore, the use of ICD-10 C-codes and V193 codes allows for an accurate definition of cancer. The following exclusion criteria were used: 1) diagnostic code of C254 (malignant neoplasm of endocrine pancreas); 2) history of any type of cancer (ICD-10: C00-97) in the 3 years prior to the date of pancreatic cancer diagnosis; 3) missing data (body mass index [BMI], alcohol, and smoking); 4) T1D (ICD-10: E10) without pancreatitis or type 1 diabetes before pancreatitis; and 5) concurrent diagnosis of diabetes and pancreatitis within 3 months before the index date or hospital visits in 2002 for both chronic pancreatitis and diabetes. In the latter case, it was not possible to determine which disease preceded the other because the database used in this study did not contain claims data before 2002.

B. Control selection

First, we selected patients with newly diagnosed pancreatic cancer from 2007 to 2021 and excluded patients who met the exclusion criteria. We then matched patients with pancreatic cancer to patients without pancreatic cancer by birth, sex, and length of follow-up at a ratio of 1:100. A total of 6,071,491 observations were matched with 60,716 patients with pancreatic cancer. After incidence density sampling, we excluded observations in the control group that met the exclusion criteria and conducted 1:9 simple random sampling. Finally, the control group included 546,444 observations.

Figure 1 Flowchart of the study inclusion and exclusion criteria



3. Definition of the index date and covariates

A. Index date

Diabetes and pancreatitis were only considered if they were diagnosed before the index date. We defined the index date as 1 year prior to the date of pancreatic cancer diagnosis, because pancreatitis and diabetes can be symptoms of pancreatic cancer development.[26,27]

Although the main analyses all set the index date as 1 year prior to the date of diagnosis of pancreatic cancer, in the analysis that further divided the groups according to duration of diabetes, pancreatitis duration, and interval period of diabetes and pancreatitis, the index date was defined as the date of diagnosis of pancreatic cancer to include new-onset disease.

B. DM

Patients with diabetes were defined if antidiabetic drugs were prescribed in combination with the presence of the ICD-10 code for diabetes (ICD-10: E10-14) from inpatient or outpatient NHIS claims data.[28] Patients with diabetes were defined as those without a type 1 diabetes diagnostic code (ICD-10: E10) before the index date in a predefined DM group.

C. Pancreatitis

Pancreatitis was confirmed when the ICD-10 code for pancreatitis was used, when acute pancreatitis (ICD-10: K85) was stated either as 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.

D. Categorizing subgroups

We divided the patients into five non-overlapping groups based on the grouping in a previous study.[21,29,30] The type 2 diabetes alone (T2D-only) group included patients who were diagnosed with type 2 diabetes,[28] and had never been diagnosed with pancreatitis prior to the index date; the pancreatitis alone (PAN-only) group included patients who were diagnosed with pancreatitis and had never been diagnosed with diabetes prior to the index date; the pancreatitis after type 2 diabetes (T2D-PAN) group included patients who were diagnosed with pancreatitis at least 90 days after type 2 diabetes diagnosis; and the post-pancreatitis DM (PPDM) group included patients 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.

The risk of pancreatic cancer was also analyzed in the subgroups. The PPDM, T2D-PAN, and T2D-only groups were further subdivided by (1) insulin use (user/non-user) and (2) duration of diabetes. The PPDM, T2D-PAN, and Pan-only groups were further subdivided by (1) acute, chronic, and recurrent (AP, acute pancreatitis without preexisting chronic pancreatitis; CP, chronic pancreatitis without acute pancreatitis; and APCP, chronic pancreatitis with acute pancreatitis episodes), (2) alcohol-related, gallstone-related (in AP), smoking-related (in CP) and other causes, and (3) duration of pancreatitis. Patients were classified as having alcohol-related pancreatitis if they had a history of drinking (moderate of heavy drinker) prior to the diagnosis of pancreatitis, and as having smoking-related pancreatitis if they had a history of smoking (past or current smoker) prior to the diagnosis of pancreatitis. In addition, patients were categorized as having gallstone-related pancreatitis if they underwent a gallstone-related procedure or surgery within 3 months of their pancreatitis diagnosis. The classification of the disease subtypes and the use of medication were both based on the index date. Additional analyses for the interval between diabetes and pancreatitis and duration of diabetes and pancreatitis were performed by including only diabetes and pancreatitis 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 to include new-onset DM and new-onset pancreatitis with a duration of less than 1 year.

4. Statistical analysis

We first compared the baseline characteristics of the case and control groups based on the diagnosis, using χ^2 tests for categorical variables and t-tests for continuous variables. Baseline characteristics consisting of continuous variables are presented as means ± SDs, and categorical variables are presented as numbers (%).

We performed analyses using a conditional logistic regression model to determine

whether the T2D-only, PAN-only, T2D-PAN, or PPDM groups was associated with a higher risk of pancreatic cancer than that related to the NDNP group. Multiple logistic regression analysis was performed using body mass index (BMI), tobacco use, and alcohol consumption. SAS version 9.3 (SAS Institute, Cary, NC) was used for data analysis.

III. RESULTS

1. Baseline characteristics

As shown in Table 1, in the majority of cases, pancreatic cancer was diagnosed in people aged > 70 years, and men were more frequently diagnosed 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). All groups except the NDNP group had a higher mean age in the group without pancreatic cancer and a lower percentage of older adults in the group with pancreatic cancer (Table 2).

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

Variables	Case (n= 60,716)	Control (n= 546,444)	*p-value*
Age at index date (years)			
Mean±SD	69±11	69±11	1.000
<40	337 (0.6)	3,033 (0.6)	
40–50	2,945 (4.9)	26,505 (4.9)	
50–60	9,514 (15.7)	85,626 (15.7)	
60–70	17,068 (28.1)	153,612 (28.1)	
70–80	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
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
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)			
Mean±SD	24.1±3.2	24.0±3.2	0.005
<18.5	1,960 (3.2)	16,750 (3.1)	<0.001
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)	
Household income			
Missing	976	9,152	0.558
Low	7,735 (12.9)	68,629 (12.8)	
Mid-low	8,481 (14.2)	76,219 (14.2)	
Middle	12,726 (21.3)	114,171 (21.2)	
Mid-high	12,885 (21.6)	117,270 (21.8)	
High	17,913 (30.0)	161,003 (30.0)	
CCI			
0	47,572 (78.4)	447,740 (81.9)	<0.001
1	5,830 (9.6)	46,199 (8.5)	
2	3,228 (5.3)	23,714 (4.3)	
≥3	4,086 (6.7)	28,791 (5.3)	

Data are presented as the mean ± standard deviation for continuous variables and n(%) for categorical variables. Statistical comparisons were performed using the t-test for continuous variables, and the $\chi 2$ test for categorical variables. Statistically significant values are indicated in bold ($p < 0.05$).

BMI, body mass index; CCI, Charlson comorbidity index

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

	Control observations					
Variables	**NDNP (n=447,125)**	**PPDM (n=719)**	**T2D-PAN (n=1,201)**	**PAN-only (n=5,790)**	**T2D-only (n=91,609)**	***p-value***
Age at index date (years)						
Mean±SD	68±11	73±9	75±9	73±10	72±9	<0.001
<40	2,996 (0.7)	0	1 (0.1)	11 (0.2)	25 (0)	<0.001
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)	<0.001
Female	205,204 (45.9)	262 (36.4)	487 (40.5)	2,404 (41.5)	40,322 (44.0)	

Variables	Pancreatic cancer cases					*p-value*
	NDNP (n=43,685)	**PPDM (n=327)**	**T2D-PAN (n=566)**	**PAN-only (n=1,655)**	**T2D-only (n=14,483)**	
Age at index date (years)						
Mean±SD	68±12	69±11	72±10	69±12	71±9	<0.001
<40	315 (0.7)	0	0	11 (0.7)	11 (0.1)	<0.001
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)	<0.001
Female	20,185 (46.2)	97 (29.7)	199 (35.2)	620 (37.5)	6530 (45.1)	

Data are presented as the mean ± standard deviation for continuous variables and n(%) for categorical variables. Statistical comparisons were performed using the t-test for continuous variables, and the $\chi 2$ test for categorical variables. Statistically significant values are indicated in bold ($p < 0.05$).

2. Association between diabetes or pancreatitis and pancreatic cancer risk

In the conditional logistic regression analysis, PPDM and T2D-PAN were significantly associated with pancreatic cancer, with a higher odds ratio than those for the T2D-only and PAN-only groups. As with the simple logistic regression, the adjusted odds ratios (AORs) were significantly higher in the T2D-only (AOR 1.65; 95% confidence interval [CI], 1.61–1.68), PAN-only (AOR, 2.96; 95% CI, 2.80–3.13]), T2D-PAN (AOR, 4.96; 95% CI, 4.48–5.49]) and PPDM (AOR, 4.71; 95% CI, 4.12–5.37]) groups than in the NDNP group (Figure 2). Both current smoker and heavy drinker status were significantly associated with the incidence of pancreatic cancer (Figure 2).

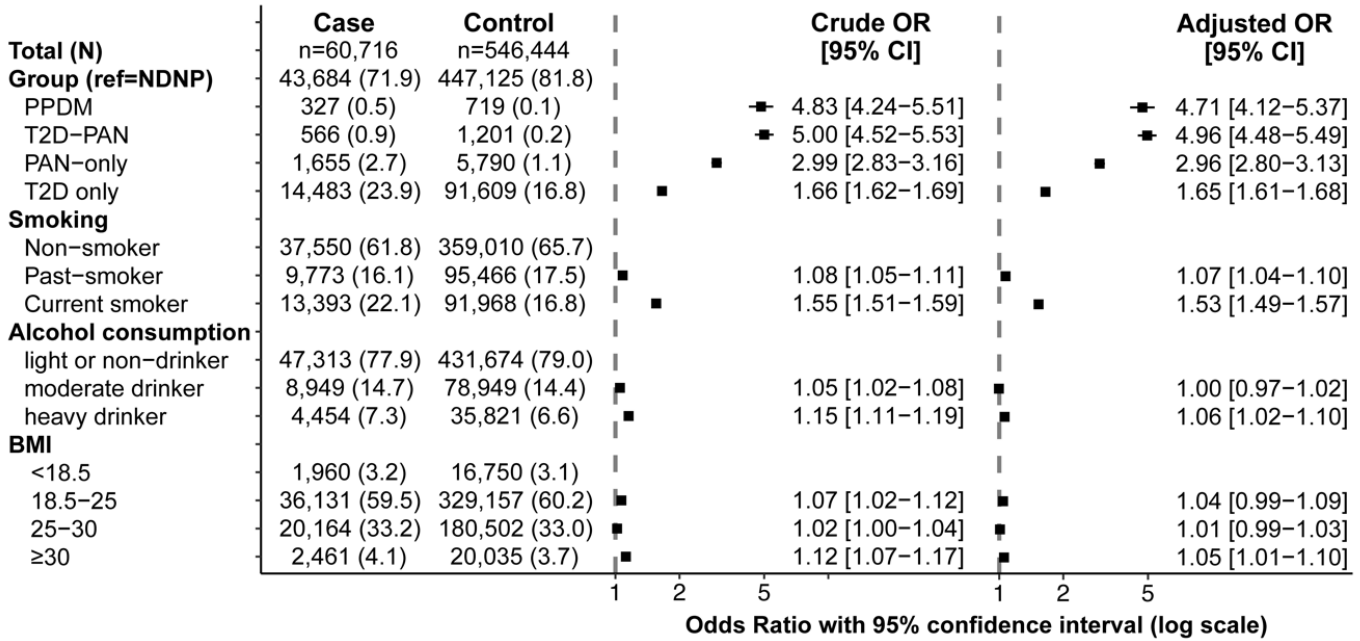
We conducted analyses by alternately using the T2D-only and PAN-only groups as the reference. Among the five groups, both PPDM and T2D-PAN were associated with the risk of developing pancreatic cancer, and the risk was significantly higher than that for PAN-only or T2D-only (Table 3).

Table 3. Multivariable logistic regression with reference replaced by the T2D-only and PAN-only groups

	Crude OR	**Adjusted OR** [a]
Ref. T2D-only		
PPDM vs. T2D-only	2.92 [2.56–3.33]	2.86 [2.50–3.26]
T2D-PAN vs. T2D-only	3.02 [2.73–3.34]	3.01 [2.72–3.33]
PAN-only vs. T2D-only	1.80 [1.70–1.91]	1.80 [1.70–1.91]
Ref. PAN-only		
PPDM vs. PAN-only	1.62 [1.40–1.86]	1.59 [1.38–1.83]
T2D-PAN vs. PAN-only	1.67 [1.49–1.88]	1.67 [1.49–1.88]

[a] Adjusted for smoking history, alcohol consumption and BMI.

Figure 2. Crude ORs (95% CIs) and adjusted ORs for the association between pancreatic cancer and categorized disease groups



[a] Adjusted for smoking history, alcohol consumption and BMI.

3. DM subgroup with a high pancreatic cancer risk

Additional analyses were conducted in the T2D-only, PPDM, and T2D-PAN groups to include variables related to patients with DM, such as the number and type of antidiabetic medications used and the duration of DM. The PPDM and T2D-PAN groups still had a higher risk of pancreatic cancer after adjusting for the additional variables. With regard to medication use, insulin use was associated with a significantly higher risk of pancreatic cancer, with combination therapy being more associated with pancreatic cancer risk than monotherapy. A shorter duration of diabetes was associated with a higher risk of pancreatic cancer (Figure 3).

Further analysis of the PPDM, T2D-PAN, and T2D-only groups by insulin use showed that in all cases, insulin use was associated with a higher AOR than no insulin use (Table 4). In particular, the insulin-using PPDM group had a 9-fold increased risk of pancreatic cancer compared to the NDNP group, and the insulin-using T2D-PAN group had a more than 6-fold increased risk compared to the NDNP group. In addition, the risk of pancreatic cancer tended to be higher in diabetics using insulin than in those not using insulin in all subgroups.

In the direct comparisons, no significant difference was observed between the PPDM and T2D-PAN groups (AOR, 0.95; 95% CI, 0.81–1.12). In addition, PPDM on insulin tended to have a higher risk of pancreatic cancer than T2D-PAN on insulin, but this difference was not statistically significant (AOR, 1.49; 95% CI, 0.97–2.29) (Table 5).

Figure 3. Logistic regression model with variables related to the treatment of patients with diabetes in the T2D-only, PPDM, and T2D-PAN groups

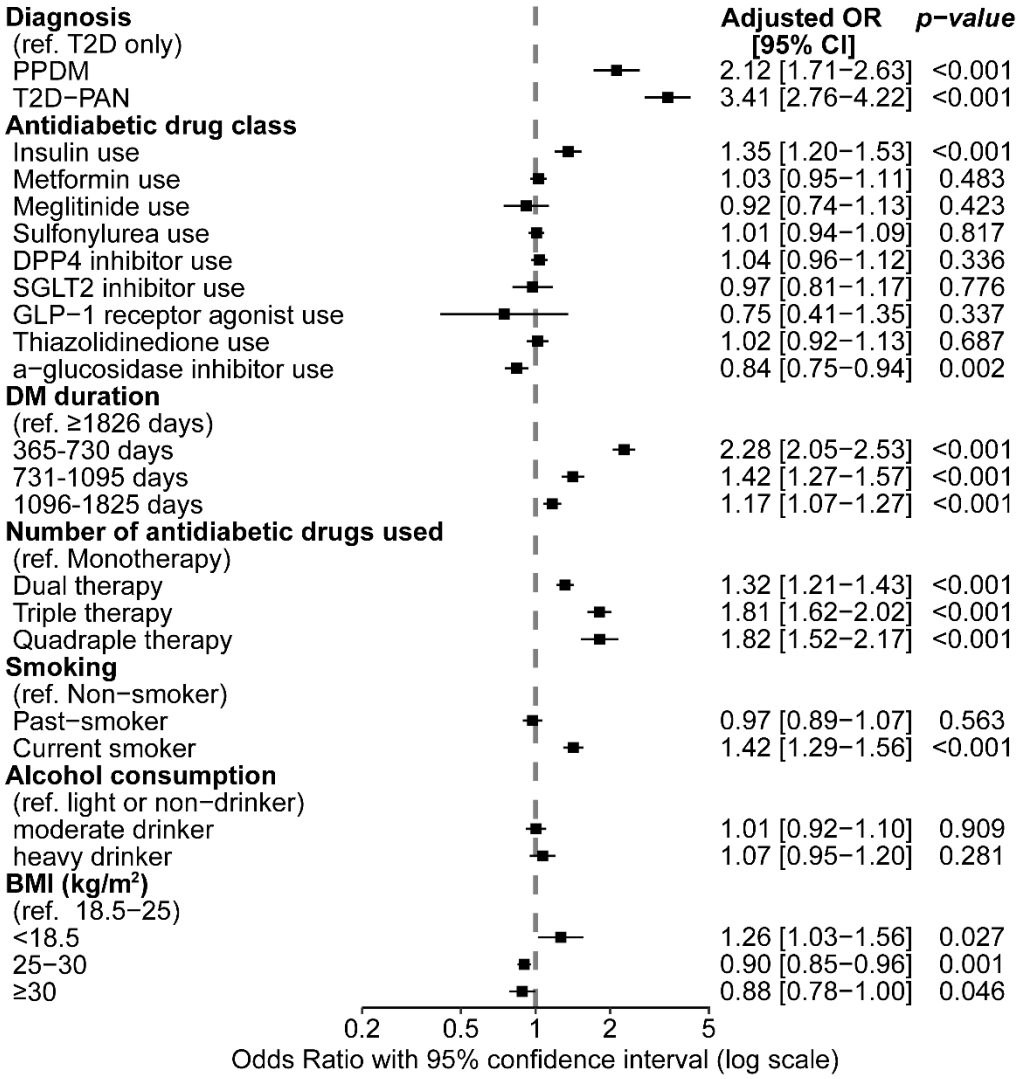


Table 4. Association between pancreatic cancer risk and disease groups further categorized by insulin use

Group	Case	Control	Crude OR	Adjusted OR[a]
NDNP	43,684 (71.9)	248,512 (81.9)	Ref.	Ref.
PPDM				
insulin use (-)	271 (0.5)	664 (0.1)	4.36 [3.78–5.02]	4.26 [3.70–4.92]
insulin use (+)	56 (0.09)	56 (0.01)	10.45 [7.21–15.14]	9.84 [6.77–14.29]
T2D-PAN				
insulin use (-)	429 (0.7)	983 (0.2)	4.63 [4.13–5.19]	4.59 [4.09–5.15]
insulin use (+)	137 (0.23)	218 (0.04)	6.67 [5.38–8.26]	6.62 [5.33–8.20]
T2D-only				
insulin use (-)	12,687 (20.9)	83,386 (15.3)	1.59 [1.56–1.63]	1.59 [1.55–1.62]
insulin use (+)	1,796 (3)	8,223 (1.5)	2.29 [2.18–2.42]	2.28 [2.17–2.41]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

Table 5. Head-to-head comparison of PPDM vs. T2D-PAN and PPDM with insulin use vs. T2D-PAN with insulin use

	Crude OR	Adjusted OR [a]
PPDM		
vs. T2D-PAN (ref)	0.97 [0.82–1.14]	0.95 [0.81–1.12]
PPDM & insulin use (+)		
vs. T2D-PAN & insulin use (+) (ref)	1.57 [1.02–2.41]	1.49 [0.97–2.29]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

We further subdivided the PPDM and T2D-only groups according to duration of diabetes and found that new-onset type 2 diabetes (DM duration < 365 days) was associated with a higher risk of pancreatic cancer than long-standing type 2 diabetes (DM duration > 1825 days) (AOR 9.10; 95% CI, 8.74–9.48 vs. AOR 1.71; 95% CI, 1.66–1.76) (Table 6).

Table 6. Association between pancreatic cancer risk and disease groups further categorized by duration of diabetes

	Crude OR	**Adjusted OR** [a]
NDNP	Ref.	Ref.
PPDM		
DM duration < 365 days	26.61 [21.06–33.62]	26.54 [20.99–33.56]
DM duration 365–730 days	9.94 [7.18–13.75]	9.79 [7.07–13.57]
DM duration 730–1095 days	9.05 [6.14–13.34]	8.83 [5.99–13.01]
DM duration 1095–1825 days	5.60 [4.08–7.69]	5.43 [3.95–7.46]
DM duration >1825 days	4.59 [3.57–5.91]	4.51 [3.50–5.81]
T2D only		
DM duration < 365 days	9.10 [8.74–9.47]	9.10 [8.74–9.48]
DM duration 365–730 days	2.96 [2.79–3.13]	2.97 [2.80–3.14]
DM duration 730–1095 days	2.14 [2.00–2.28]	2.15 [2.01–2.29]
DM duration 1095–1825 days	1.75 [1.66–1.84]	1.76 [1.67–1.85]
DM duration >1825 days	1.71 [1.65–1.76]	1.71 [1.66–1.76]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

4. Pancreatitis subgroup with high pancreatic cancer risk

Acute pancreatitis without recurrence was associated with the lowest risk of pancreatic cancer in the PPDM, T2D-PAN, and PAN-only groups, whereas acute pancreatitis with preexisting chronic pancreatitis or chronic pancreatitis with preexisting acute pancreatitis was associated with the highest risk of pancreatic cancer. The risk of pancreatic cancer was comparable between chronic pancreatitis and recurrent acute pancreatitis (Table 7).

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

	Crude OR	Adjusted OR [a]
NDNP	Ref.	Ref.
PPDM		
AP (1 episode)	2.75 [2.16–3.52]	2.72 [2.13–3.48]
AP (≥2 episodes)	4.88 [3.26–7.33]	4.83 [3.22–7.25]
CP	4.11 [3.22–5.24]	4.03 [3.16–5.14]
APCP	13.51 [10.31–17.70]	12.69 [9.68–16.65]
T2D-PAN		
AP (1 episode)	3.65 [3.10–4.30]	3.61 [3.06–4.25]
AP (≥2 episodes)	5.45 [3.75–7.91]	5.47 [3.76–7.95]
CP	5.64 [4.82–6.60]	5.62 [4.80–6.58]
APCP	9.39 [7.04–12.52]	9.19 [6.89–12.27]
PAN only		
AP (1 episode)	2.12 [1.94–2.31]	2.10 [1.93–2.29]
AP (≥2 episodes)	4.02 [3.34–4.85]	3.97 [3.29–4.79]
CP	3.08 [2.80–3.40]	3.08 [2.79–3.39]
APCP	7.36 [6.39–8.46]	7.22 [6.27–8.31]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

In the PPDM, T2D-PAN and PAN alone groups, gallstone-related acute pancreatitis was associated with a lower risk of pancreatic cancer than acute pancreatitis from other causes or alcohol-related acute pancreatitis (Table 8). In the PPDM group, alcohol-related chronic pancreatitis was associated with a higher risk of pancreatic cancer than smoking-related chronic pancreatitis; however, in the T2D-PAN group, the risk of pancreatic cancer was similar for smoking-related and alcohol-related chronic pancreatitis (Table 8).

The T2D-PAN and PAN-only groups were further subdivided according to pancreatitis duration, and new-onset pancreatitis was associated with a higher risk of pancreatic cancer (Table 9).

Table 8. Association between pancreatic cancer risk and disease groups further categorized by pancreatitis cause

	OR [95% CI] [a]		**OR [95% CI]** [a]
NDNP	Ref.	**NDNP**	Ref.
PPDM (Acute)		**PPDM (Chronic)**	
Other causes	5.51 [4.59-6.62]	Other causes	6.16 [5.05-7.52]
Alcohol-related	8.99 [5.17-15.64]	Alcohol-related	7.38 [2.34-23.27]
Gallstone-related	3.24 [2.22-4.73]	Smoking-related	8.31 [5.44-12.71]
Alcohol & gallstone -related	8.42 [1.88-37.74]	Alcohol & smoking -related	15.39 [6.90-34.34]
T2D-PAN (Acute)		**T2D-PAN (Chronic)**	
Other causes	5.32 [4.58-6.19]	Other causes	5.85 [4.99-6.85]
Alcohol-related	5.01 [2.97-8.44]	Alcohol-related	3.31 [1.41-7.76]
Gallstone-related	2.64 [1.93-3.63]	Smoking-related	9.23 [6.68-12.75]
Alcohol & gallstone -related	5.58 [1.02-30.50]	Alcohol & smoking -related	8.92 [4.24-18.77]
PAN only (Acute)		**PAN only (Chronic)**	
Other causes	3.11 [2.88-3.36]	Other causes	3.60 [3.29-3.94]
Alcohol-related	5.07 [3.95-6.52]	Alcohol-related	4.21 [2.71-6.53]
Gallstone-related	1.94 [1.64-2.29]	Smoking-related	5.96 [4.88-7.27]
Alcohol & gallstone -related	3.22 [1.64-6.33]	Alcohol & smoking -related	5.94 [4.08-8.65]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

Table 9. Association between pancreatic cancer risk and disease groups further categorized by duration of pancreatitis

	Crude OR	Adjusted OR [a]
NDNP	Ref.	Ref.
T2D-PAN		
PAN duration < 365 days	67.40 [56.15–80.91]	66.68 [55.53–80.08]
PAN duration 365–730 days	10.11 [7.81–13.09]	9.83 [7.59–12.74]
PAN duration 730–1095 days	5.48 [4.00–7.51]	5.45 [3.97–7.47]
PAN duration 1095–1825 days	5.50 [4.23–7.14]	5.49 [4.22–7.13]
PAN duration >1825 days	4.01 [3.19–5.05]	3.97 [3.16–5.00]
PAN only		
PAN duration < 365 days	52.39 [47.81–57.41]	51.67 [47.15–56.63]
PAN duration 365–730 days	5.92 [5.13–6.84]	5.85 [5.06–6.76]
PAN duration 730–1095 days	4.04 [3.42–4.76]	3.99 [3.38–4.71]
PAN duration 1095–1825 days	3.65 [3.19–4.17]	3.60 [3.15–4.12]
PAN duration >1825 days	2.44 [2.23–2.68]	2.42 [2.21–2.66]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

5. Pancreatic cancer risk based on interval between diabetes and pancreatitis

In both the PPDM and T2D-PAN groups, the shorter the time between diabetes and pancreatitis diagnosis, the higher the risk of developing pancreatic cancer. In the T2D-PAN group, the risk of developing pancreatic cancer was approximately 20 times higher than that in the NDNP group if diabetes developed < 1 year or ≥ 5 years of pancreatitis diagnosis (Table 10). In the PPDM group, the risk of pancreatic cancer was higher when diabetes developed within a short time after the onset of pancreatitis (Table 10).

Table 10. Association between pancreatic cancer risk and the PPDM and T2D-PAN groups according to the time interval between pancreatitis and diabetes diagnosis.

	Crude OR	**Adjusted OR** [a]
NDNP	Ref.	Ref.
PPDM		
Interval time [b] < 1 year	16.05 [11.65–22.11]	15.65 [11.35–21.58]
Interval time [b] ≥ 1 year	9.21 [8.07–10.50]	9.08 [7.96–10.36]
T2D-PAN		
Interval time [c] < 1 year	21.81 [16.90–28.14]	21.64 [16.76–27.95]
Interval time [c] ≥ 1 year	15.05 [13.67–16.57]	14.87 [13.50–16.37]

[a] Adjusted for smoking history, alcohol consumption, and BMI.
[b] Time interval between the diagnosis of pancreatitis and the diagnosis of diabetes
[c] Time interval between the diagnosis of type 2 diabetes and the diagnosis of pancreatitis

6. Sensitivity analysis

The risk of pancreatic cancer was relatively higher in the PPDM, T2D-PAN, PAN-only, and T2D-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, T2D-PAN, PAN-only, and T2D-only groups maintained high ORs for pancreatic cancer when the lag period was increased to more than one year. (Table 11).

Table 11. Association between pancreatic cancer risk and disease groups according to the lag period

	Crude OR	Adjusted OR [a]
Ref. NDNP (no lag period)		
PPDM	9.17 [8.23–10.22]	9.03 [8.10–10.06]
T2D-PAN	13.88 [12.91–14.93]	13.77 [12.80–14.81]
PAN only	8.37 [8.02–8.72]	8.26 [7.92–8.61]
T2D only	2.36 [2.31–2.40]	2.36 [2.31–2.41]
Ref. NDNP (lag period: 180 days)		
PPDM	6.03 [5.33–6.82]	5.92 [5.23–6.70]
T2D-PAN	5.71 [5.20–6.28]	5.66 [5.15–6.22]
PAN only	3.33 [3.16–3.52]	3.31 [3.14–3.49]
T2D only	1.81 [1.78–1.85]	1.81 [1.77–1.85]
Ref. NDNP (lag period: 1year)		
PPDM	4.83 [4.24–5.51]	4.71 [4.12–5.37]
T2D-PAN	5.00 [4.52–5.53]	4.96 [4.48–5.49]
PAN only	2.99 [2.83–3.16]	2.96 [2.80–3.13]
T2D only	1.66 [1.62–1.69]	1.65 [1.61–1.68]
Ref. NDNP (lag period: 2 years)		
PPDM	4.25 [3.66–4.94]	4.17 [3.59–4.84]
T2D-PAN	4.29 [3.83–4.81]	4.22 [3.76–4.73]
PAN only	2.65 [2.49–2.81]	2.63 [2.48–2.79]
T2D only	1.55 [1.52–1.58]	1.54 [1.51–1.58]
Ref. NDNP (lag period: 3 years)		
PPDM	3.75 [3.18–4.43]	3.65 [3.09–4.30]
T2D-PAN	4.06 [3.58–4.61]	4.00 [3.53–4.54]
PAN only	2.51 [2.36–2.68]	2.49 [2.34–2.66]
T2D only	1.52 [1.49–1.55]	1.51 [1.48–1.55]
Ref. NDNP (lag period: 5 years)		
PPDM	3.85 [3.14–4.73]	3.77 [3.07–4.64]
T2D-PAN	3.20 [2.74–3.74]	3.18 [2.72–3.71]
PAN only	2.39 [2.22–2.57]	2.36 [2.20–2.54]
T2D only	1.50 [1.47–1.54]	1.50 [1.46–1.53]

[a] Adjusted for smoking history, alcohol consumption, and BMI.

IV. DISCUSSION

1. Summary of the main findings

In this study, compared to the NDNP group, both the T2D-only and the PAN-only groups showed a significantly increased risk of pancreatic cancer. In addition, both the T2D-PAN and PPDM groups had a significantly higher risk of pancreatic cancer than the T2D-only or PAN-only groups. These results suggest that type 2 diabetes and pancreatitis are independent risk factors for pancreatic cancer, and that having both diseases is associated with a higher risk of pancreatic cancer than having only one disease. In this study, the PPDM group showed a significantly increased risk of pancreatic cancer compared to the PAN-only and T2D-only groups, consistent with the findings of a previous study. The main finding of our study was that the co-existence of diabetes and pancreatitis, such as in the PPDM group or T2D-PAN group, increased the risk of pancreatic cancer more than the T2D-only and PAN-only groups.

2. High-risk subgroups for pancreatic cancer

A. DM

We further analyzed the PPDM, T2D-PAN, and T2D-only groups according to insulin use, and found that those who used insulin before the index date had a significantly higher risk of pancreatic cancer than those who did not use insulin. The reason for this could be that the use of insulin indicates difficulty in controlling blood sugar, which may reflect the increased risk of pancreatic cancer in patients with poor glycemic control. Particularly in the PPDM group, which is associated with an approximately 9-fold increased risk of pancreatic cancer compared to the NDNP group, (AOR, 9.27; 95% CI, 5.78–14.85) suggesting that careful surveillance for pancreatic cancer may be warranted in PPDM patients with insulin use.

B. Pancreatitis

We further analyzed the PPDM, T2D-PAN, and PAN-only groups according to pancreatitis status. Analyses that subdivided the disease group by pancreatitis status showed similar results to previous studies.[10] In each group, recurrent acute pancreatitis or chronic pancreatitis tended to increase the risk of pancreatic cancer compared to only one episode of acute pancreatitis. This suggests that in the PPDM, T2D-PAN, and PAN-only groups, patients with recurrent acute pancreatitis or chronic pancreatitis should be more concerned about the development of pancreatic cancer.

Additionally, we analyzed the PPDM, T2D-PAN, and PAN-only groups according to pancreatitis causes. Previous studies have shown a higher risk of pancreatic cancer in idiopathic pancreatitis than in gallstone-related pancreatitis.[10,31] Similar to previous studies, we found that the adjusted OR was higher in the PPDM, T2D-PAN, and PAN-only groups with acute pancreatitis due to other causes than in those with gallstone-related pancreatitis. This study also analyzed the risk of pancreatic cancer based on the cause of chronic pancreatitis. As a result, the PPDM groups and T2D-PAN groups with smoking-related chronic pancreatitis demonstrated more than a 9-fold increased risk of pancreatic cancer.

C. Duration and interval of diabetes and pancreatitis

In disease groups that included new-onset diabetes or new-onset pancreatitis, the risk of pancreatic cancer was significantly higher than that in the NDNP group. In the PPDM group, shorter duration of diabetes was significantly associated with the development of pancreatic cancer. In addition, in the T2D-PAN group, more recent pancreatitis was significantly associated with the development of pancreatic cancer. These results are closely related to reverse causality, which is discussed later in Section 4.

In the PPDM and T2D-PAN groups, the risk of pancreatic cancer varied according to the interval between diabetes and pancreatitis, particularly in the PPDM group, where the risk of pancreatic cancer was 15 times higher than that in the NDNP group if diabetes developed within 1 year of pancreatitis diagnosis. Although the evidence 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, (5) alterations in the insulin-incretin axis, or a combination of these factors.[32] This is likely because in diabetes that occurred after pancreatitis, the interval reflects the severity of the pancreatitis.

3. Reverse causality

Because high blood glucose levels 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, 74–88% of patients are diagnosed with diabetes within 24 months following their diagnosis of pancreatic ductal adenocarcinoma.[33] High serum glucose levels may be one of the symptoms of pancreatic cancer, and the following explanatory mechanisms have been proposed to explain this: 1) diabetogenic factors secreted by the pancreatic tumor may reduce insulin secretion and sensitivity[34] and 2) beta-cell dedifferentiation by pancreatic cancer may cause beta-cell dysfunction, leading to hyperglycemia.[35]

Furthermore, it is not known how many years it takes for symptoms to appear after pancreatic cancer develops.[36,37] Therefore, when diabetes or pancreatitis is diagnosed before pancreatic cancer is diagnosed, it is difficult to determine exactly whether it occurred before or after pancreatic cancer. In previous studies analyzing the relationship between diabetes or pancreatitis and pancreatic cancer, various lag periods were applied to exclude reverse causality.[5,13]

In this 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. In the sensitivity analysis, T2D-only, PAN-only, T2D-PAN, and PPDM were significantly associated with an increased risk of pancreatic cancer compared to NDNP, although the

highest OR was observed without a lag period. Therefore, patients with new-onset disease may have a significantly higher correlation with pancreatic cancer, which is consistent with the results of previous studies.[38] However, diabetes and pancreatitis remained significantly associated with pancreatic cancer risk even as the lag period increased, suggesting the continued surveillance for the development of pancreatic cancer, even if it was not new-onset.

4. Novelty of this research

A. Differences from previous studies

When directly comparing the T2D-PAN and PPDM groups, no significant difference was observed (AOR, 1.01; 95 % CI, 0.84–1.22), and the T2D-PAN group was associated with a significantly higher risk of pancreatic cancer than the PAN-only group. The order of disease onset did not significantly contribute to the risk of pancreatic cancer in patients with coexisting diabetes and pancreatitis.

These results were inconsistent with those of a previous study in which the PAN-only and T2D-PAN groups had similar pancreatic cancer risks, and the PPDM group had a significantly higher pancreatic cancer risk than the T2D-PAN group.[21] 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. Secondly, the distinction in study design played a significant role. T2D-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.[39]

B. Identifying subgroups at increased risk of pancreatic cancer

In patients with diabetes, new-onset diabetes is the most recognized subgroup with a higher risk of pancreatic cancer.[40-44] One research attempted to identify a high-risk subgroup using a model based on a combination of weight change and glycemic change in patients with new-onset diabetes.[41] In this study, we added additional factors related to pancreatic cancer, such as pancreatitis, and further subdivided them using the cause of pancreatitis, usage of insulin, duration of diabetes, and interval between pancreatitis and diagnosis of diabetes, and tried to identify subgroups with higher risk of pancreatic cancer.

5. Clinical relevance

Screening is suggested in high-risk populations, including individuals with a >5% lifetime risk, or five-fold increased relative risk (RR), as proposed by international cancer of the pancreas screening.[16] PPDM was associated with a more than 8-fold increased risk of pancreatic cancer compared to NDNP for up to 3 years after diabetes onset. T2D-PAN was associated with a 9-fold increased risk of pancreatic cancer compared to NDNP up to 2 years after pancreatitis. Additionally, PPDM with insulin use was associated with a 9-fold increased risk of pancreatic cancer, and T2D-PAN with insulin use was associated with a 6-fold increased risk of pancreatic cancer. As shown in the results listed above, this study identified several subgroups of patients with diabetes and pancreatitis whose risk of pancreatic cancer was more than five times higher than that of the general population. The increased risk of pancreatic cancer in insulin use and new-onset DM is most likely due to reverse causality.[38,45] However, these findings suggest that pancreatic cancer is more likely to be detected at screening in the high-risk subgroup identified in this study. In addition, sensitivity analysis with different lag periods confirmed that PPDM, T2D-PAN, PAN-only, and T2D-only groups were still risk factors for pancreatic cancer after excluding the effect of reverse causality, suggesting that clinicians should still pay attention to these patients.

6. Strengths and limitations

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. Patients with pancreatic cancer can only register for this program if their diagnosis is confirmed by one of the following methods: 1) histologic examination, 2) cytologic examination, 3) imaging and biochemical/immunologic/hematologic tests, or 4) imaging and diagnostic surgery without histologic examination. These criteria ensure a more accurate definition of cancer diagnosis despite relying solely on insurance claims data. Additionally, utilizing the NDNP group as a reference enabled the evaluation of pancreatic cancer risk in the T2D-only, PAN-only, T2D-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. First, the histological type and stage of pancreatic cancer were not included in the NHID; therefore, these data could not be considered in our study. Second, although the study was designed as a nested case-control design, during the data collection process, raw data for the entire Korean population were unavailable due to data capacity limitations; therefore, incidence density sampling was performed with age- and sex-matched sampled data. As a result, the case group diagnosed with pancreatic cancer was excluded from the incidence density sampling used to extract the control group. However, because the incidence of pancreatic cancer is low, we do not expect this step to have a significant impact on the results.[39] Third, because this study was a retrospective cohort study, a well-designed prospective study is needed to accurately identify the causal relationship between PPDM and pancreatic cancer.

V. CONCLUSION

In conclusion, using the Korean nationwide cohort study data, we demonstrated that the T2D-PAN and PPDM groups were more associated with a higher risk of pancreatic cancer than the T2D-only and PAN-only groups. Because PPDM accounts for the second highest proportion of diabetes after T2D,[46] efforts should be made not miss the diagnosis of patients with PPDM at the point of care. In addition, pancreatitis in patients with type 2 diabetes is associated with an increased risk of pancreatic cancer and should be considered in follow-up. Because the PPDM and T2D-PAN groups using insulin or having a short time interval between pancreatitis and diabetes had a significantly higher risk of pancreatic cancer than the NDNP group, more aggressive pancreatic cancer screening should be considered in these patients.

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ABSTRACT(IN KOREAN)

빅데이터 분석을 통한 췌장암 발생에 있어서 췌장염과 2형 당뇨병의 역할

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목표: 췌장암은 사망률이 높지만 발병률은 낮기 때문에 일반인에게는 선별검사를 권장하지 않고 고위험군에게만 선별검사진행을 권고하고 있다. 국제 췌장암 검진 컨소시엄에서는 평생에 걸쳐 췌장암 발생률이 5%를 넘거나, 일반인 대비 상대 위험도가 5배 이상인 특정 환자군에서의 선별검사를 권고하고 있다. 따라서 췌장암 검진을 통해 실보다는 득이 더 많은 고위험군을 식별하는 것은 중요한 과제이다. 당뇨병과 췌장염이 췌장암의 위험 요인으로 알려져 있음에도 불구하고, 췌장암 발생 위험이 췌장암 선별검사를 권고할 만큼 높지는 않기 때문에 검진 대상에 포함되지 않는다. 본 연구는 당뇨병 및 췌장염 환자군 중에서 췌장암 검진을 고려할 고위험군 환자를 식별하는 것이 목표이다.

연구 방법: 2002년부터 2021년 사이에 한국 국민건강보험공단이 모은 국민건강정보데이터를 제공받아 분석하였다. 대조군은 2007년부터 2021년까지 췌장암을 새로 진단받은 환자들로 구성되었으며, 추적관찰기간, 성별, 나이를 기준으로 대조군을 선별하였다. 환자들은 기준일에 따라 2형당뇨병만 있는 군 (type 2 diabetes-only, T2D-only), 췌장염만 있는 군 (pancreatitis-only, PAN-only), 2형당뇨병 이후 췌장염 발생한 군 (pancreatitis after type 2 diabetes, T2D-PAN), 췌장염이후 당뇨병이 발생한 군 (post-pancreatitis diabetes mellitus, PPDM), 당뇨병 및 췌장염 모두 진단된 적 없는 군 (no diabetes and no

pancreatitis, NDNP)으로 분류되었다. 조건부 로지스틱 회귀 분석을 이용하여 위에서 분류한 각 군이 NDNP군과 비교하여 췌장암 발병 위험이 몇 배 증가하는지 분석하였다.

결과: 2형당뇨병과 췌장염은 췌장염의 독립적인 위험 인자로 밝혀졌으며, 이 두 가지가 동시에 존재할 경우 췌장암 발생 위험이 추가적으로 더 높아졌다. 조건부 로지스틱 회귀 분석에서 T2D-only (조정된 오즈비 [AOR] 1.65; 95 % 신뢰구간 [CI] 1.61-1.68), PAN-only (AOR 2.96; 95 % CI, 2.80-3.13), T2D-PAN (AOR 4.96; 95% CI, 4.48-5.49) 및 PPDM(AOR 4.71; 95% CI, 4.12-5.37)군 모두에서 NDNP 군보다 유의하게 췌장암 위험이 더 높았다. 이 네개의 군 중 T2D-PAN 및 PPDM 군은 T2D 단독 및 PAN 단독 그룹에 비해서도 췌장암 발생 위험과의 연관성이 유의하게 더 높았다. 그러나 T2D-PAN 군과 PPDM 군 간 췌장암 위험에는 유의한 차이가 나타나지 않았다 (AOR, 0.95; 95 % CI, 0.81-1.12). 당뇨병 환자 중 인슐린을 사용한 경우 인슐린을 사용하지 않은 환자에 비해 췌장암 위험이 더 높았으며, 당뇨병과 췌장염이 동시에 발생한 그룹에서는 두 질환 간의 진단 사이 기간이 1년이내로 짧은 더 높은 췌장암 발생 위험과 관련됨을 확인할 수 있었다.

결론: PPDM 및 T2D-PAN 그룹은 T2D 단독 및 PAN 단독 그룹 및 일반 인구에 비해 췌장암 위험이 유의하게 높았다. 특히나 PPDM 및 T2D-PAN 그룹에서 인슐린을 사용하거나 당뇨병과 췌장염 발생 간격이 짧은 경우 일반인구대비 5배 이상 높은 췌장암 발생 위험을 보였다. 그 외에도 췌장염 원인에 따라, 당뇨병 및 췌장염 발생 한 뒤 경과한 기간에 따라 다양한 췌장암 발생 위험을 보였다. 따라서 본 연구를 통해 해당 하위그룹에서 적극적인 췌장암 선별 검사를 고려하는 것을 제안하는 바이다.

핵심되는 말 :
췌장염 이후 당뇨병, 2형당뇨병 이후 췌장염, 2형당뇨병, 췌장염, 췌장암