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Clinical Research Article

Difference of Risk of Pancreatic Cancer in New-Onset Diabetes and Long-standing Diabetes: A Population-based Cohort Study

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Abstract

Context: Considering the absence of methods to find pancreatic cancer early, surveillance of high-risk groups is needed for early diagnosis.

Objective: The study aimed to investigate the effect in the incidence of pancreatic cancer and the differences between new-onset diabetes mellitus (NODM) and long-standing DM (LSDM) since NODM group is a representative high-risk group.

Methods: The Korean National Health Insurance Service–National Sample Cohort between 2002 and 2013 data were used. Regarding 88 396 people with DM (case group), we conducted a 1:1 propensity score matching to select a matched non-DM population (control group). To investigate the interaction between DM and the time variable distinguishing NODM and LSDM, we performed a multivariate time-dependent Cox regression analysis.

Results: The incidence of pancreatic cancer was higher in the DM group compared to the non-DM group (0.52% vs 0.16%; $P < .001$). The DM group had shown different risk of pancreatic cancer development according to the duration since the DM diagnosis (NODM hazard ratio (HR): 3.81; 95% CI, 2.97-4.88; $P < .001$; LSDM HR: 1.53; 95% CI, 1.11-2.11; $P < .001$). When the NODM and the LSDM groups were compared, the risk of pancreatic cancer was higher in the NODM group than in the LSDM group (HR: 1.55; $P = .020$). In subgroup analysis, NODM group showed that men (HR = 4.42; 95% CI, 3.15-6.19; $P < .001$) and patients who were in their 50 seconds (HR = 7.54; 95% CI, 3.24-17.56; $P < .001$) were at a higher risk of developing pancreatic cancer than matched same sex or age control group (non-DM population), respectively.

Conclusion: The risk of pancreatic cancer was greater in people with DM than in a non-DM population. Among people with DM, NODM showed a higher risk of pancreatic cancer than LSDM.

Key Words: pancreatic cancer, new-onset DM, long-standing DM, early diagnosis

Abbreviations: CCI, Charlson comorbidity index; DM, diabetes mellitus; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; LSDM, long-standing diabetes mellitus; NHIS, National Health Insurance Service; NIIS-NSC, National Health Insurance Service–National Sample Cohort; NODM, new-onset diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; PSM, propensity score matching; PY, person-year.

Pancreatic cancer has a dismal prognosis because cancer-specific symptoms occur only at an advanced stage. Curative resection is possible in only 10% to 20% of people with pancreatic cancer (1). Early detection of pancreatic cancer is essential to improve overall survival. However, the incidence of pancreatic cancer is low, and screening the general population is neither cost-effective nor practical. Therefore, it is important to know the high-risk group for the development of pancreatic cancer (2-5).

Previous data suggest that diabetes mellitus (DM) is associated with pancreatic cancer (6-8). At the time of their diagnosis, 30% to 50% of newly diagnosed people with pancreatic cancer are also found to have diabetes. In particular, pancreatic cancer–associated DM occurs within 2 or 3 years before

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the diagnosis of cancer. Previous studies reported that DM is paraneoplastic phenomena induced by pancreatic cancer. Adrenomedullin was shown to mediate pancreatic cancer–induced inhibition of insulin secretion in β cells in various in vitro and in vivo orthotopic and subcutaneous tumor models (9). Older patients with new-onset DM (NODM) have an approximately 8-fold higher risk of having pancreatic cancer than the general population (10-12). Therefore, recognition of NODM as an early manifestation of pancreatic cancer implies that it can be a predictive diagnostic factor for pancreatic cancer. On the other hand, long-standing DM (LSDM) is also a risk factor for pancreatic cancer. The mechanism is associated with the tumorigenic effect of chronic hyperglycemia (13).

Most available data for pancreatic cancer-related NODM have come from Western countries, while nationwide population-based studies for NODM in pancreatic cancer are rare in Asia. Moreover, there were limited studies comparing the risk of NODM and LSDM on pancreatic cancer. Here, we aimed to examine the association between DM and pancreatic cancer through comparing the risk in NODM and the risk in LSDM using data from a nationwide population-based cohort.

Materials and Methods

Data Source

Korea provides universal health insurance service through the Korean National Health Insurance Service (NHIS) under the government's supervision. The NHIS is the single-payer that collects insurance claim data of all Korean citizens including sociodemographic data, diagnostic, treatment, and health examination–related data. Based on the collected data, NHIS established databases since 2002 and the NHIS–National Sample Cohort (NHIS-NSC) is one data set. The NHIS-NSC selected 2.2% of the entire Korean population and followed individuals for 11 years (14). Among the entire population, a systematic, stratified, random-sampling method considering age, sex, income level, and medical expense was applied to select the population for NHIS-NSC (14). Thus, the data have been described as representative data for Korean population health.

This was reviewed and approved by the institutional review board of Yonsei University Health System (institutional review board No. 4-2020-1032).

Study Population

To select the study population, we applied a washout period of 2 years from 2002 to 2003 to obtain newly diagnosed individuals with DM and pancreatic cancer. There was a total of 396 patients with the pancreatic cancer diagnostic code during the 2-year washout period. Our study population was diagnosed from 2004 onward. The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) was used to identify people with type 2 DM (E11) and people with pancreatic cancer (C25). Also, we excluded patients younger than 30 years, who are less likely to be diagnosed with pancreatic cancer.

For the case group, 88 396 diabetic patients were selected. Based on those patients, we conducted 1:1 propensity score matching (PSM) of age, sex, and year in which DM was diagnosed to select a control group (non-DM group, patients not diagnosed with DM). Regarding the index date of the control group, the index date (follow-up start date) for each matched pair's DM date was assigned as their index date. Thus, matched pairs have the same index date. After PSM, we excluded 416 participants in the control group who had pancreatic cancer before the index date. Thus, we obtained 87 980 control group individuals, bringing the total study population to 176 376 participants after PSM.

Definition of Diabetes Mellitus Classification

The patients in the new-onset DM (NODM) and long-standing DM (LSDM) groups are defined by the duration since DM diagnosis. As per NODM, if the patients were diagnosed DM for 3 years or less, then they were classified into the NODM group, while patients with LSDM had been diagnosed for DM more than 3 years. Thus, the study population in the NODM group was 29 382 individuals, while the LSDM group included 59 014 individuals. The variable follow-up period after DM diagnosis indicates the NODM and LSDM. Thus, DM × follow-up period after DM diagnosis presents the β value of interaction between 2 variables. Regarding the definition of NODM, we referenced recent retrospective and prospective studies (10, 12, 15-19).

Variables

Pancreatic cancer was defined using the ICD-10 code C25. Factors that we included for the study were sex, age, region, health insurance type, income level, diagnosis of chronic pancreatitis, Charlson comorbidity index (CCI), and cohort entry year. The age groups were divided into 10-year intervals: 30 to 39, 40 to 49, 50 to 59, 60 to 69, and older than 70. The regions were grouped into capital (Seoul), metropolitan area (Busan, Daegu, Daejeon, Gwangju, Incheon, and Ulsan), and rural area (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju). Diagnosis of pancreatitis was given at baseline with the ICD-10 code K86. The CCI was defined as previously described by Charlson et al (20) to predict risk of death within 1 year of hospitalization for patients with multiple comorbid conditions. High score was associated with impaired mortality compared with patients with a low-grade score.

Statistical Analyses

Frequencies and percentages of each variable are presented. Chi-square tests were performed to compare differences in variables and incidence of pancreatic cancer at the baseline of the study. As for the analysis, we used a multivariate Cox proportional-hazards model to estimate adjusted hazard ratios (HRs) and 95% CIs to investigate associations between variables and survival time. For the main analysis, time-dependent survival analysis was applied to calculate the interaction between NODM and non-NODM. All analyses were performed using SAS software, version 9.4 (SAS Institute). Kaplan-Meier curves were conducted using the "survival" package in R 3.3.2.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the study population. A total of 176 376 participants (DM group, n = 88 396 and non-DM group, n = 87 980) were enrolled in this study. Out of these, 596 participants (0.34%) were diagnosed with pancreatic cancer. In people with DM, the case group, 458 patients (0.52%) were diagnosed with pancreatic cancer—346 patients in the NODM group and 112 patients in the LSDM group. The incidence of pancreatic cancer in the case group was higher than that in the matched control group (0.52% vs 0.16%; $P < .001$). Of the total participants, 0.60% (n = 1066) had chronic pancreatitis, and the incidence of pancreatic cancer among chronic pancreatitis was higher than those without chronic pancreatitis (6.75% vs 0.30%; $P < .001$).

Incidence Rate of Pancreatic Cancer in Population With Diabetes Mellitus

The incidence rate of pancreatic cancer per 100 000 person-year (PY) is shown in Table 2. The person-year of case group was 429 232, while it was 441 439 for the control group. The incidence rate of pancreatic cancer per 100 000 PY for the case group was 106.7, while the control group had 31.3 ($P < .001$). For the NODM population, the PY of case group was 221 011 and its incidence rate of pancreatic cancer per 100 000 was 156.6 (control group: 34.9; $P < .001$). With regard to the LSDM population, the person-year of case group was 208 221 and its incidence rate of pancreatic cancer per 100 000 was 53.8 (control group: 27.5; $P < .001$).

Diabetes Mellitus as a Risk Factor for Pancreatic Cancer Development

Kaplan-Meier curves (Fig. 1) indicate that the case group (people with DM) were at a higher risk of developing pancreatic cancer than the control group (non-DM population) ($P < .001$) in both the NODM and LSDM groups. Table 3 contains the results of Cox proportional-hazards model, exhibiting the HRs between patient variables and pancreatic cancer in total years, within 3 years (NODM), and after 3 years (LSDM) of diagnosis of DM from the result of the analyses in total years. Participants who were in the case group (people with DM) showed a higher risk of developing pancreatic cancer than the control group (non-DM population) (HR = 2.80; 95% CI, 2.31-3.40; $P < .001$). The following groups showed a higher risk of developing pancreatic cancer: male patients (HR = 1.66; 95% CI, 1.41-1.96; $P < .001$), older participants (age > 70 years: HR = 14.13; 95% CI, 6.26-31.89; $P < .001$), and people with chronic pancreatitis (HR = 15.17; 95% CI, 11.83-19.46; $P < .001$).

Among the NODM group, the case group (people with DM) had a higher risk of developing pancreatic cancer than the control group (non-DM population) (HR = 3.81; 95% CI, 2.97-4.88, $P < .001$). In particular, more than 10 times the incidence rate of pancreatic cancer was found for those older than 60 years or who were diagnosed with chronic pancreatitis. Similarly, in the LSDM group, the case group (people with DM) had a higher risk of developing pancreatic cancer compared with the control group (non-DM population) (HR = 1.53; 95% CI, 1.11-2.11; $P = .009$). Also, those older than 60 years or who were diagnosed with chronic pancreatitis showed an increased risk of developing pancreatic cancer.

Higher Incidence Rate of Pancreatic Cancer in New-Onset Diabetes Mellitus

To investigate the interaction between DM and the time variable that distinguishes NODM from LSDM, we performed a multivariate, time-dependent Cox regression analysis with the interaction between NODM and LSDM (Table 4). The results showed a difference in the risk of pancreatic cancer between the NODM group and LSDM group in that the NODM group had a higher risk for pancreatic cancer development than the LSDM group (HR = 1.55; $P = .020$). Table 5 shows the results of the subgroup analysis of people with pancreatic cancer according to sex, age, diagnosis of chronic pancreatitis, CCI, and income level. The results from the NODM group showed that men (HR = 4.42; 95% CI, 3.15-6.19; $P < .001$) and patients who were in their 40s (HR = 12.08; 95% CI, 2.80-52.07; $P < .001$) and 50s (HR = 7.54; 95% CI, 3.24-17.56; $P < .001$) were at a higher risk of developing pancreatic cancer than a matched same sex or age control group (non-DM population), respectively. In the subgroup analysis on the interaction between DM and the time variable, male patients (HR = 1.69; $P = .040$), patients in younger age groups (30s: HR = 2.63; $P = .557$; 40s: HR = 1.16; $P = .417$; 50s: HR = 2.07; $P = .114$), people with chronic pancreatitis (HR = 1.83; $P = .274$), and patients in the CCI group "0" (HR = 5.97; $P = .266$) had a higher risk of pancreatic cancer than matched non-DM group. Of course, as shown in clinical practice, the actual incidence of pancreatic cancer in older individuals was much higher than in younger people in this study. When the incidence of pancreatic cancer in the NODM group was compared to the non-DM group of the same age, NODM alone made relatively little contribution to pancreatic cancer development than age because there are various factors that can influence the development of pancreatic cancer in older patients.

Discussion

In this large, sampled, longitudinal and retrospective study to investigate the risk of pancreatic cancer, we examined the association between DM and pancreatic cancer. Furthermore, we compared the risk of pancreatic cancer development between NODM and LSDM. As a result, the case group diagnosed with DM had an increased risk of pancreatic cancer (HR = 2.80; 95% CI, 2.31-3.40; $P < .001$). The risk of pancreatic cancer in individuals who were diagnosed DM for 3 years or less (NODM) was higher than in individuals who had DM for more than 3 years (LSDM) with an HR of 1.55. In particular, early identification of pancreatic cancer is important because the only curative treatment option, surgical resection, is possible in its earlier stages. In this study, the surgical resection rate was higher in pancreatic cancer in the NODM group (8.09%, 28/346) than pancreatic cancer in the LSDM group (1.79%, 2/112).

The prevalence of DM was higher in patients with pancreatic cancer than in patients with other types of cancers (21). Hyperglycemia, insulin resistance, and impaired pancreatic β-cell function are all considered biological conditions that induce proliferation of malignant pancreatic cells (22). Moreover, DM is commonly associated with

Table 1. General characteristics of the study population

Variables	Study population n = 176 376 (n,%)	Patients with pancreatic cancer n = 596 (n,%)	*P*
Diabetes mellitus			< .001
Case	88 396 (50.118)	458 (0.518)	
Control	87 980 (49.882)	138 (0.157)	
Sex			.001
Male	90 210 (51.146)	347 (0.385)	
Female	86 166 (48.854)	249 (0.289)	
Age, y			< .001
30-39	14 747 (8.361)	6 (0.041)	
40-49	34 803 (19.732)	39 (0.112)	
50-59	48 464 (27.478)	101 (0.208)	
60-69	42 692 (24.205)	217 (0.508)	
> 70	35 670 (20.224)	233 (0.653)	
Region			.975
Capital	35 156 (19.932)	121 (0.344)	
Metropolitan	44 552 (25.260)	150 (0.337)	
Rural	96 668 (54.808)	325 (0.336)	
Health insurance			.870
Self-employed health insurance	61 989 (35.146)	205 (0.331)	
Employee health insurance	105 943 (60.067)	364 (0.344)	
Medical aid	8444 (4.787)	27 (0.320)	
income level			.003
1Q (lowest)	33 488 (18.987)	92 (0.275)	
2Q	38 436 (21.792)	127 (0.330)	
3Q	52 385 (29.701)	162 (0.309)	
4Q (highest)	52 067 (29.520)	215 (0.413)	
Chronic pancreatitis			< .001
Yes	1066 (0.604)	72 (6.754)	
No	175 310 (99.396)	524 (0.299)	
CCI			< .001
0	24 567 (13.929)	18 (0.073)	
1	24 651 (13.976)	28 (0.114)	
2	27 614 (15.656)	33 (0.120)	
3	99 544 (56.439)	517 (0.519)	
Cohort entry year			< .001
2004	19 406 (11.003)	103 (0.531)	
2005	20 467 (11.604)	79 (0.386)	
2006	16 642 (9.436)	75 (0.451)	
2007	17 218 (9.762)	68 (0.395)	
2008	18 197 (10.317)	60 (0.330)	
2009	16 907 (9.586)	62 (0.367)	
2010	15 463 (8.767)	42 (0.272)	
2011	18 262 (10.354)	42 (0.230)	
2012	17 123 (9.708)	37 (0.216)	
2013	16 691 (9.463)	28 (0.168)	

Abbreviation: CCI, Charlson comorbidity index.

obesity and metabolic syndrome, and both conditions increase the risk of developing cancer. In this study, the risk of developing pancreatic cancer was 2.8 times greater in the DM group than in the matched non-DM group. This result was consistent with data from previous reports. Previously published literature demonstrated an overall approximate 2-fold increased risk of pancreatic cancer in people with DM (23-25).

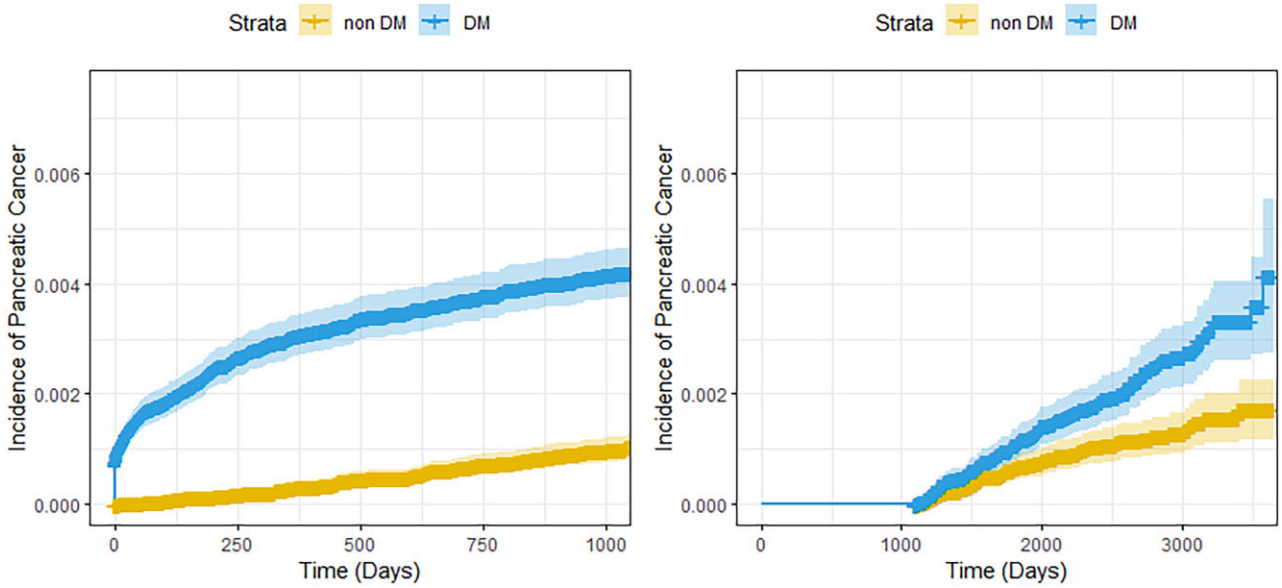

Figure 1. Risk of pancreatic cancer in new-onset diabetes mellitus (NODM) and long-standing diabetes mellitus (LSDM) patients. A, NODM; B, LSDM.

Conversely, DM could be a consequence of pancreatic cancer. In a previous study, about 60% of people with pancreatic cancer with NODM who had surgical resection had resolution of their DM after tumor removal. These findings imply that NODM in pancreatic cancer is likely caused by the tumor (26). Several studies have offered additional evidence for this idea, demonstrating that tumor removal improves glucose tolerance and can even correct the metabolic abnormality (17, 27, 28). Regarding the hypothesis that DM is a consequence of pancreatic cancer, various experimental studies have suggested that pancreatic cancer–associated DM is a paraneoplastic condition produced by tumor-secreted chemicals. Metabolically active pancreatic cancer cell line supernatants have been demonstrated to produce glucose intolerance in SCID animals, affecting glucose metabolism in the liver and skeletal muscle (17, 29-33). Based on these findings, NODM is thought to be an early manifestation of asymptomatic pancreatic cancer, and it has been proposed as a potential early detection marker for this fatal cancer (17, 26, 34-36). A previous study showed that hyperglycemia precedes diagnosis of pancreatic cancer by approximately 36 months, providing a possible window of opportunity for the early detection of pancreatic cancer in people with NODM (2). However, the association between NODM and pancreatic cancer is not well understood. In the present study, among the NODM group, the case group (DM) had a 3.8 times higher risk of pancreatic cancer than the control group (non-DM) ($P < .001$). In addition, the risk of pancreatic cancer among the NODM group and LSDM group revealed that the NODM group had a 1.55 times higher risk of pancreatic cancer than the LSDM group ($P = .020$). Previously, Chari et al (12) reported that an NODM group had an 8-fold higher risk of pancreatic cancer than individuals from the general population (non-DM). Huang et al (37) showed that an NODM group had an almost 7-fold increase in risk of pancreatic cancer compared with a non-DM group. Most available data for pancreatic cancer-related NODM have come from Western countries, while nationwide population-based studies for NODM in pancreatic cancer are rare in Asia. Although the Huang study included an Asian population, it included only 19 people with NODM.

Table 2. Incidence rate of pancreatic cancer per person-years

Variables	Total		Pancreatic cancer		
	N (%)	PY	Yes (n, %)	Incidence rate[a]	*P*
Total					< .001
Case	88 396 (50.12)	429 232	458 (0.52)	106.70	
Control	87 980 (49.88)	441 439	138 (0.16)	31.26	
NODM					< .001
Case	88 396 (50.12)	221 011	346 (0.39)	156.55	
Control	87 980 (49.88)	223 564	78 (0.09)	34.89	
LSDM					< .001
Case	59 014 (49.42)	208 221	112 (0.19)	53.79	
Control	60 411 (50.58)	217 875	60 (0.10)	27.54	

Abbreviations: LSDM, long-standing diabetes mellitus; NODM, new-onset diabetes mellitus; PY, person-year.
[a]Incidence rate of pancreatic cancer per 100 000 PYs.

Table 3. Multivariate Cox regression analysis of risk factors for pancreatic cancer development

Variables	Pancreatic cancer								
	Total			NODM			Non-NODM		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Diabetes mellitus									
Yes	2.80	(2.31-3.40)	< .001	3.81	(2.97-4.88)	< .001	1.53	(1.11-2.11)	.009
No	1.00		Ref.	1.00		Ref.	1.00		Ref.
Sex									
Male	1.66	(1.41-1.96)	< .001	1.72	(1.41-2.09)	< .001	1.50	(1.11-2.04)	.009
Female	1.00		Ref.	1.00		Ref.	1.00		Ref.
Age, y									
30-39	1.00		Ref.	1.00		Ref.	1.00		Ref.
40-49	2.35	(1.00-5.56)	.051	3.60	(1.10-11.83)	.035	1.13	(0.31-4.13)	.849
50-59	4.31	(1.89-9.83)	.001	6.00	(1.89-19.09)	.002	2.62	(0.80-8.56)	.112
60-69	9.81	(4.35-22.10)	< .001	14.55	(4.63-45.71)	< .001	5.06	(1.58-16.20)	.006
70+	14.13	(6.26-31.89)	< .001	19.96	(6.35-62.81)	< .001	8.19	(2.55-26.31)	.000
Region									
Capital	1.06	(0.86-1.30)	.613	0.98	(0.76-1.27)	.885	1.23	(0.85-1.77)	.274
Metropolitan	1.08	(0.89-1.32)	.414	1.16	(0.93-1.46)	.190	0.89	(0.61-1.32)	.570
Rural	1.00		Ref.	1.00			1.00		Ref.
health insurance									
Self-employed	1.00		Ref.	1.00		Ref.	1.00		Ref.
Employee	1.04	(0.87-1.23)	.686	1.12	(0.91-1.37)	.301	0.86	(0.63-1.18)	.354
Medical aid	1.20	(0.75-1.93)	.437	0.88	(0.49-1.59)	.678	2.41	(1.11-5.23)	.027
income level									
1Q (lowest)	0.70	(0.53-0.92)	.012	0.73	(0.52-1.01)	.059	0.64	(0.38-1.06)	.083
2Q	1.01	(0.81-1.26)	.963	0.99	(0.76-1.30)	.949	1.04	(0.70-1.54)	.855
3Q	0.87	(0.71-1.07)	.179	1.01	(0.80-1.29)	.920	0.56	(0.37-0.85)	.007
4Q (highest)	1.00		Ref.	1.00		Ref.	1.00		Ref.
Chronic pancreatitis									
Yes	15.17	(11.83-19.46)	< .001	14.79	(11.0-19.88)0	< .001	16.44	(10.35-26.10)	< .001
No	1.00		Ref.	1.00		Ref.	1.00		Ref.
CCI									
0	0.32	(0.20-0.52)	< .001	0.40	(0.24-0.68)	.001	0.15	(0.05-0.49)	.002
1	0.38	(0.26-0.55)	< .001	0.39	(0.25-0.62)	< .001	0.33	(0.16-0.68)	.003
2	0.35	(0.24-0.49)	< .001	0.41	(0.28-0.61)	< .001	0.20	(0.09-0.45)	< .001
3	1.00		Ref.	1.00		Ref.	1.00		Ref.
Cohort entry year									
2004	1.00		Ref.	1.00		Ref.	1.00		Ref.
2005	0.80	(0.60-1.08)	.145	0.61	(0.40-0.93)	.022	1.09	(0.71-1.66)	.707
2006	1.01	(0.75-1.37)	.936	1.09	(0.75-1.59)	.638	0.84	(0.49-1.42)	.514
2007	0.94	(0.69-1.30)	.723	0.75	(0.50-1.13)	.174	1.35	(0.82-2.22)	.244
2008	0.85	(0.61-1.19)	.337	0.84	(0.56-1.24)	.372	0.80	(0.43-1.48)	.482
2009	1.08	(0.78-1.50)	.650	0.97	(0.66-1.43)	.876	1.38	(0.72-2.66)	.331
2010	0.95	(0.65-1.38)	.787	0.90	(0.60-1.34)	.591	0.66	(0.15-2.85)	.581
2011	0.94	(0.65–1.38)	.759	0.90	(0.60-1.35)	.613			
2012	1.09	(0.73–1.62)	.671	1.02	(0.67-1.55)	.922			
2013	1.48	(0.95-2.30)	.084	1.37	(0.86-2.18)	.184			

Abbreviations: CCI, Charlson comorbidity index; HR, hazard ratio; LSDM, long-standing diabetes mellitus; NODM, new-onset diabetes mellitus; Ref., reference.

Table 4. Result of time-dependent Cox regression analysis on new-onset diabetes mellitus patients compare with long-standing diabetes mellitus patients

Variables	Pancreatic cancer		
	HR	*P*	95% CI
DM			
Yes	1.51	.010	
No	Ref.		
Follow-up period after DM diagnosis			
Within 3 y	0.78	.153	
After 3 y	Ref.		
Diabetes × follow-up period after DM diagnosis	1.55	.020	
Sex			
Male	1.58	< .001	(1.36-1.84)
Female	Ref.		
Age, y			
30-39	Ref.		
40-49	1.73	.134	(0.84-3.55)
50-59	3.24	.001	(1.64-6.40)
60-69	7.46	< .001	(3.83-14.54)
70+	10.60	< .001	(5.43-20.68)
Region			
Capital	1.14	.174	(0.94-1.37)
Metropolitan	0.99	.877	(0.82-1.19)
Rural	Ref.		
Health insurance			
Self-employed health insurance	Ref.		
Employee health insurance	1.00	.996	(0.85-1.17)
Medical aid	1.54	.039	(1.02-2.33)
income level			
1Q (lowest)	0.69	.004	(0.53-0.89)
2Q	1.05	.632	(0.86-1.28)
3Q	0.78	.011	(0.64-0.94)
4Q (highest)	Ref.		
Pancreatitis			
Yes	14.95	< .001	(11.87-18.82)
No	Ref.		
CCI			
0	0.27	< .001	(0.17-0.42)
1	0.36	< .001	(0.25-0.51)
2	0.27	< .001	(0.19-0.39)
3	Ref.		
Cohort entry year			
2004	Ref.		
2005	0.74	.019	(0.58-0.95)
2006	0.60	< .001	(0.46-0.79)
2007	0.60	< .001	(0.46-0.79)
2008	0.45	< .001	(0.33-0.60)
2009	0.51	< .001	(0.38-0.69)
2010	0.34	< .001	(0.24-0.48)
2011	0.58	.007	(0.39-0.86)
2012	0.70	.088	(0.46-1.06)
2013	0.93	.784	(0.57-1.54)

Abbreviations: CCI, Charlson comorbidity index; DM, diabetes mellitus; HR, hazard ratio; Ref., reference.

Table 5. Subgroup analysis on pancreatic cancer by sex, age, chronic pancreatitis, Charlson comorbidity index, and income level

Variables	Total		*P*	NODM[a]		*P*	Non-NODM[b]		*P*	DM × follow-up period after DM diagnosis	
	HR	95% CI		HR	95% CI		HR	95% CI		HR	*P*-value
Sex											
Male	3.15	(2.43-4.10)	< .001	4.42	(3.15-6.19)	< .001	1.59	(1.03-2.46)	.381	1.69	0.040
Female	2.40	(1.80-3.19)	< .001	3.13	(2.17-4.53)	< .001	1.45	(0.90-2.33)	.125	1.38	0.246
Age, y											
30-39	4.41	(0.48-40.30)	.189	N/A	—		2.35	(0.19-28.60)	.503	2.63	0.557
40-49	10.54	(3.17-35.07)	< .001	12.08	(2.80-52.07)	< .001	7.27	(0.86-61.47)	.069	1.16	0.417
50-59	3.41	(2.01-5.79)	< .001	7.54	(3.24-17.56)	< .001	1.25	(0.59-2.67)	.560	2.07	0.114
60-69	2.05	(1.52-2.76)	< .001	2.54	(1.76-3.68)	< .001	1.23	(0.73-2.08)	.433	1.41	0.264
70+	3.03	(2.24-4.10)	< .001	4.05	(2.75-5.97)	< .001	1.71	(1.03-2.85)	.040	1.55	0.143
Chronic pancreatitis											
Yes	2.10	(1.16-3.78)	.014	2.90	(1.33-6.29)	.007	1.10	(0.42-2.90)	.820	1.83	0.274
No	2.87	(2.34-3.52)	< .001	3.87	(2.98-5.04)	< .001	1.54	(1.10-2.17)	.009	1.53	0.034
CCI											
0	35.55	(4.69-269.34)	< .001	N/A	—		8.47	(0.65-109.65)	.098	5.97	0.266
1	3.23	(1.45-7.21)	.004	4.51	(1.62-12.52)	.004	2.15	(0.47-9.83)	.427	1.43	0.665
2	5.16	(2.23-11.99)	< .001	5.74	(2.16-15.22)	< .001	5.38	(0.72-40.21)	.216	1.26	0.811
3	2.44	(1.99-3.00)	< .001	3.26	(2.50-4.25)	< .001	1.40	(1.00-1.96)	.060	1.51	0.038
Income level											
1Q (lowest)	2.69	(1.64-4.40)	< .001	3.41	(1.79-6.48)	< .001	1.93	(0.87-4.31)	.117	1.28	0.592
2Q	2.51	(1.67-3.78)	< .001	3.73	(2.15-6.48)	< .001	1.29	(0.67-2.46)	.432	1.75	0.144
3Q	3.43	(2.30-5.10)	< .001	3.96	(2.48-6.30)	< .001	2.02	(0.92-4.43)	.083	1.38	0.461
4Q (highest)	2.63	(1.92-3.59)	< .001	3.78	(2.50-5.73)	< .001	1.31	(0.79-2.15)	.351	1.53	0.155

Abbreviations: CCI, Charlson comorbidity index; DM, diabetes mellitus; HR, hazard ratio; N/A, not applicable; NODM, new-onset diabetes mellitus; Ref., reference.

Pancreatic cancer–associated DM may occur because of gland destruction caused by pancreatic cancer or insulin resistance caused by tumor-secreted products (38). More frequently, it may occur because of long-standing insulin resistance related to overweight and unhealthy habits. It is possible that individuals with existing insulin resistance and an inflammatory state associated with obesity are more susceptible to the extra stress of pancreatic tissue damage caused by the tumor (39). Previous studies reported that the pancreas was more fragile to outside stimuli in Asian populations. A smaller pancreas, a limited innate capacity for insulin secretion, and higher fat deposition might be critical causes of vulnerability to DM in Asian people compared with White people with similar body mass index and body fat levels (40). Because of this vulnerability, its function is easily decreased by β-cell exhaustion because of continuous insulin resistance (41). Therefore, it is meaningful to investigate the effect of NODM on the incidence of pancreatic cancer in the Asian population.

In this study, NODM may be one of the high-risk groups for pancreatic cancer since there is no definitive early-detection tool and population for sporadic pancreatic cancer. But routine checkups with expensive tools may not relevant because of the small fraction of people with pancreatic cancer among people with DM, even if that is higher than the general population. Targeted screening for pancreatic cancer may be feasible if diabetic individuals at the highest risk for pancreatic cancer–associated DM could be identified. In the present data, when combined with chronic pancreatitis, 8.1% (58/716) patients were diagnosed with pancreatic cancer. Among them, 75.8% (44/58) occurred in an NODM period. When combined with patients aged 50 years like in other prospective trials (NCT03731637, NCT03937453), 0.66% (417/63 608) of patients were diagnosed with pancreatic cancer. Among them, 75.7% (316/417) occurred in an NODM period. When combined with chronic pancreatitis and age older than 50 years, the incidence of pancreatic cancer was 9.85% (52/528) in the present study. Most patients' (73%) cases also occurred in the NODM period. We assume that combination of age (> 50 years), chronic pancreatitis history, and NODM may be more relevant for finding pancreatic cancer in the clinical field.

In this study, an urban population (capital and metropolitan) showed an increased risk of pancreatic cancer development, an HR greater than 1, compared to a rural population in people with DM after multivariate Cox regression analysis. In previous studies, cancer incidence rates were generally higher in urban populations (42). This also applies to pancreatic cancer. Baum et al (43, 44) reported that the incidence rates of pancreatic cancer were 1.3 to approximately 2 times

higher in urban compared to rural areas. Blot et al (45) also showed that the rates for pancreas cancer were higher in urban areas, especially in males. These findings were assumed to be related to socioeconomic development, increased smoking rates, Westernized diets, lack of exercise, increased diabetes, changes in the urban environment, and improvement in diagnosis.

There are several limitations to the present study. First, this study used claims data that has only diagnostic data. Thus, cancer-related factors, such as family history, obesity, and smoking history, were not included in this study. And, the present study used diagnostic codes with 3 digits that could not distinguish the region of pancreatic cancer. Therefore, we suggest conducting further investigations, including those specific factors of pancreatic cancer, using another data set. However, we have adjusted for CCI, which provides information about chronic respiratory disease closely related to smoking and chronic pancreatitis as high-risk factors for pancreatic cancer. Second, pancreatic cancer in this study includes a broader scope of pancreatic cancer. Therefore, we have further analyzed patients with pancreatic ductal adenocarcinoma (PDAC) only, which had shown a similar outcome (Supplementary Tables 1 and 2) (46). The NODM group had a 1.55 times higher risk of PDAC than the LSDM group ($P = .020$). Last, as the data are health insurance data, all people with DM in our study were diagnosed with DM. The Korean insurance system is managed by a single insurer (NHIS), which is compulsory for all citizens and health care facilities. Thus, once the patient visits any doctor and is diagnosed with DM, he or she will be in the system, NHIS claim data. This means that the individual who is grouped as non-DM is never diagnosed with DM. However, it is possible that we grouped individuals who have DM but never went to see a doctor as a non-DM patient. This is one of the study limitations from the data.

In conclusion, the risk of pancreatic cancer was greater in people with DM than in a general population. Among people with DM, the NODM group showed a higher risk of pancreatic cancer than the LSDM group.

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Author Contributions

All authors have read and agreed to the published version of the manuscript. Conceptualization: H.S.L., M.J.S., J.K., J.H.J., M.J.C., and SB; data curation: W.C., E.C.P., and S.I.J.; formal analysis: W.C., C.M.N., and S.I.J.; investigation: H.S.L., W.C., M.J.S., J.K., J.H.J., M.J.C., J.Y.P., S.W.P., S.Y.S., E.C.P., S.I.J., and S.B.; methodology: W.C., C.M.N., and S.I.J.; validation: J.Y.P., S.W.P., and S.Y.S.; wiring: H.S.L., W.C., S.I.J., and S.B.; supervision: S.I.J. and S.B.

Disclosures

The authors have nothing to disclose.

Data Availability

Available on request to NHIS (https://nhiss.nhis.or.kr) for research purposes only. Analytic methods will be available on request to the corresponding authors.

References

1. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med*. 2014;371(11):1039-1049.
2. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol*. 2009;10(1):88-95.
3. Pereira SP, Oldfield L, Ney A, *et al*. Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2020;5(7):698-710.
4. Kanno Y, Koshita S, Ogawa T, *et al*. Predictive value of localized stenosis of the main pancreatic duct for early detection of pancreatic cancer. *Clin Endosc*. 2019;52(6):588-597.
5. Garg SK, Chari ST. Early detection of pancreatic cancer. *Curr Opin Gastroenterol*. 2020;36(5):456-461.
6. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. *Mol Cancer*. 2003;2(1):4.
7. Li D. Diabetes and pancreatic cancer. *Mol Carcinog*. 2012;51(1):64-74.
8. Rosato V, Tavani A, Bosetti C, *et al*. Metabolic syndrome and pancreatic cancer risk: a case-control study in Italy and meta-analysis. *Metabolism*. 2011;60(10):1372-1378.
9. Sah RP, Nagpal SJS, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol*. 2013;10(7):423-433.
10. Sharma A, Kandlakunta H, Nagpal SJS, *et al*. Model to determine risk of pancreatic cancer in patients with new-onset diabetes. *Gastroenterology*. 2018;155(3):730-739.e3.
11. Aggarwal G, Rabe KG, Petersen GM, Chari ST. New-onset diabetes in pancreatic cancer: a study in the primary care setting. *Pancreatology*. 2012;12(2):156-161.
12. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology*. 2005;129(2):504-511.
13. Song S, Wang B, Zhang X, *et al*. Long-term diabetes mellitus is associated with an increased risk of pancreatic cancer: a meta-analysis. *PLoS One*. 2015;10(7):e0134321.
14. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service–National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46(2):e15.
15. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology*. 2019;156(7):2024-2040.
16. Boursi B, Finkelman B, Giantonio BJ, *et al*. A clinical prediction model to assess risk for pancreatic cancer among patients with new-onset diabetes. *Gastroenterology*. 2017;152(4):840-850.e3.
17. Chari ST, Leibson CL, Rabe KG, *et al*. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology*. 2008;134(1):95-101.
18. Chari ST, Maitra A, Matrisian LM, *et al*; Early Detection Initiative Consortium. Early Detection Initiative: a randomized controlled trial of algorithm-based screening in patients with new onset hyperglycemia and diabetes for early detection of pancreatic ductal adenocarcinoma. *Contemp Clin Trials*. 2022;113:106659.

19. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. *Gastroenterology*. 2018;155(2):490-500.e492.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
21. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas*. 2013;42(2):198-201.
22. Rahn S, Zimmermann V, Viol F, *et al*. Diabetes as risk factor for pancreatic cancer: hyperglycemia promotes epithelial-mesenchymal-transition and stem cell properties in pancreatic ductal epithelial cells. *Cancer Lett*. 2018;415:129-150.
23. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005;92(11):2076-2083.
24. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA*. 1995;273(20):1605-1609.
25. Ben Q, Cai Q, Li Z, *et al*. The relationship between new-onset diabetes mellitus and pancreatic cancer risk: a case-control study. *Eur J Cancer*. 2011;47(2):248-254.
26. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology*. 2008;134(4):981-987.
27. Permert J, Larsson J, Fruin AB, *et al*. Islet hormone secretion in pancreatic cancer patients with diabetes. *Pancreas*. 1997;15(1):60-68.
28. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnquist HJ, Larsson J. Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. *Br J Surg*. 1993;80(8):1047-1050.
29. Basso D, Brigato L, Veronesi A, Panozzo MP, Amadori A, Plebani M. The pancreatic cancer cell line MIA PaCa2 produces one or more factors able to induce hyperglycemia in SCID mice. *Anticancer Res*. 1995;15(6B):2585-2588.
30. Basso D, Valerio A, Brigato L, *et al*. An unidentified pancreatic cancer cell product, alters some intracellular pathways of glucose metabolism in isolated rat hepatocytes. *Pancreas*. 1997;15(2):132-138.
31. Basso D, Millino C, Greco E, *et al*. Altered glucose metabolism and proteolysis in pancreatic cancer cell conditioned myoblasts: searching for a gene expression pattern with a microarray analysis of 5000 skeletal muscle genes. *Gut*. 2004;53(8):1159-1166.
32. Li J, Adrian TE. A factor from pancreatic and colonic cancer cells stimulates glucose uptake and lactate production in myoblasts. *Biochem Biophys Res Commun*. 1999;260(3):626-633.
33. Wang F, Larsson J, Abdiu A, *et al*. Dissociated secretion of islet amyloid polypeptide and insulin in serum-free culture media conditioned by human pancreatic adenocarcinoma cell lines. *Int J Pancreatol*. 1997;21(2):157-164.
34. Risch HA, Yu H, Lu L, Kidd MS. Detectable symptomatology preceding the diagnosis of pancreatic cancer and absolute risk of pancreatic cancer diagnosis. *Am J Epidemiol*. 2015;182(1):26-34.
35. Andersen D. Diabetes and cancer: placing the association in perspective. *Curr Opin Endocrinol Diabetes Obes*. 2013;20(2):81-86.
36. Gullo L, Pezzilli R, Morselli-Labate AM. Diabetes and the risk of pancreatic cancer. *N Engl J Med*. 1994;331(2):81-84.
37. Huang BZ, Pandol SJ, Jeon CY, *et al*. New-onset diabetes, longitudinal trends in metabolic markers, and risk of pancreatic cancer in a heterogeneous population. *Clin Gastroenterol Hepatol*. 2020;18(8):1812-1821.e7.
38. Liu J, Knezetic JA, Strömmer L, Permert J, Larsson J, Adrian TE. The intracellular mechanism of insulin resistance in pancreatic cancer patients. *J Clin Endocrinol Metab*. 2000;85(3):1232-1238.
39. Li D, Mao Y, Chang P, *et al*. Impacts of new-onset and long-term diabetes on clinical outcome of pancreatic cancer. *Am J Cancer Res*. 2015;5(10):3260-3269.
40. Roh E, Kim KM, Park KS, *et al*. Comparison of pancreatic volume and fat amount linked with glucose homeostasis between healthy Caucasians and Koreans. *Diabetes Obes Metab*. 2018;20(11):2642-2652.
41. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care*. 2013;36(6):1789-1796.
42. Zahnd WE, James AS, Jenkins WD, *et al*. Rural-urban differences in cancer incidence and trends in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27(11):1265-1274.
43. He Y, Zheng R, Li D, Zeng H, Zhang S, Chen W. Pancreatic cancer incidence and mortality patterns in China, 2011. *Chin J Cancer Res*. 2015;27(1):29-37.
44. Baum C, Soliman AS, Brown HE, *et al*. Regional variation of pancreatic cancer incidence in the Nile Delta region of Egypt over a twelve-year period. *J Cancer Epidemiol*. 2020;2020:6031708–6031708.
45. Blot WJ, Fraumeni JF Jr, Stone BJ. Geographic correlates of pancreas cancer in the United States. *Cancer*. 1978;42(1):373-380.
46. Lee HS, Chae W, Sung MJ, *et al*. Supplementary materials for "Difference of risk of pancreatic cancer in new-onset diabetes and long-standing diabetes: population-based cohort study." 2022. Deposited November 1, 2022. https://ir.ymlib.yonsei.ac.r/handle/22282913/190694