Nationwide Trends in Pancreatitis and Pancreatic Cancer Risk Among Patients With Newly Diagnosed Type 2 Diabetes Receiving Dipeptidyl Peptidase 4 Inhibitors

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OBJECTIVE

Dipeptidyl peptidase 4 inhibitors (DPP-4i) are useful incretin-based antidiabetes drugs. However, there is a concern that DPP-4i may adversely impact the exocrine pancreas, owing to their pleiotropic effects. In this study, we investigated whether DPP-4i are associated with pancreatitis and pancreatic cancer using a nationwide population-based cohort study.

RESEARCH DESIGN AND METHODS

We included patients newly diagnosed with type 2 diabetes who were treated with antidiabetes drugs (*n* = 33,208) from 2007 to 2013. The data were obtained from the Korean National Health Insurance Service–Health Screening Cohort database (*n* = 514,866). Risk was estimated using a Cox proportional hazards model with time-dependent covariates. A 6-month lag time was used to account for a possible latency time. The risk across various time segments since the first prescription of DPP-4i was also analyzed.

RESULTS

Out of 33,208 subjects, 10,218 were new users of DPP-4i and 22,990 were new users of other antidiabetes drugs. DPP-4i significantly increased the risks of pancreatitis (adjusted hazard ratio [aHR] 1.24, 95% CI 1.01–1.52; *P* = 0.037) and pancreatic cancer (aHR 1.81, 95% CI 1.16–2.82; *P* = 0.009) with a 6-month drug use lag period. The risk of pancreatitis and pancreatic cancer was generally consistent in the first 12 months and 1 year after the initial prescription without showing an increasing trend according to exposure duration.

CONCLUSIONS

DPP-4i use is associated with increased risks of pancreatitis and pancreatic cancer in patients with newly diagnosed type 2 diabetes. However, the absence of increasing trend according to exposure duration suggests the chances of reverse causality, and long-term pancreatic safety of DPP-4i has to be further investigated.

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Type 2 diabetes is an important risk factor for pancreatitis and pancreatic cancer (1–4). Type 2 diabetes has been associated with a 2.89-fold increase in the risk of developing acute pancreatitis (3). The incidence of pancreatic cancer has been reported to increase markedly in a population with diabetes, with a relative risk of 2.1 (1). Long-standing type 2 diabetes increases the risk of pancreatic cancer, and conversely, pancreatic cancer induces the development of diabetes (1,2).

Dipeptidyl peptidase 4 inhibitors (DPP-4i) are widely used, well-tolerated antidiabetes agents that offer several advantages in clinical settings, especially for medically fragile populations, owing to their favorable efficacy and safety profile (5). However, the possible association of DPP-4i with pancreatitis and pancreatic cancer is a rising concern (5–8). DPP-4i and glucagon-like peptide 1 (GLP-1) receptor agonists are incretin-based antidiabetes drugs. Incretin hormones, such as GLP-1, improve β-cell function and suppress glucagon secretion to ameliorate hyperglycemia (9,10). However, incretins are also known to exert pleiotropic effects on the exocrine pancreas, such as stimulation of cellular proliferation and dysplasia (11,12).

The pancreatic safety of incretin-based therapies is an important clinical issue (5–7). In a meta-analysis of large randomized controlled trials, incretin-based therapies were significantly associated with acute pancreatitis (13). In addition, a recent cohort study showed that incretin-based therapies had an adjusted hazard ratio (aHR) of 2.14 for pancreatic cancer (7). However, the pancreatic safety of DPP-4i therapy independent of other incretin-based treatments has not been adequately evaluated.

Therefore, we conducted a large nationwide population-based cohort study to investigate the risk of pancreatitis and pancreatic cancer associated with DPP-4i use in patients with newly diagnosed type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Source

The data used in the current study were extracted from the Korean National Health Insurance Service–Health Screening Cohort (NHIS-HEALS) database between 2002 and 2013 (14). The NHIS established the National Health Information Database (NHID) in 2011, using information from medical treatment and health screening records, as well as eligibility data from an existing database (15). Based on the NHID, the Korean NHIS constructed the NHIS-HEALS database, which included data of a cohort of subjects who participated in health screening programs provided by the NHIS (14). For building of the NHIS-HEALS database, a sample cohort was first obtained from 2002–2003 health screening participants. These patients were between 40 and 79 years of age in 2002 and were followed up to 2013. This cohort comprised 514,866 health screening participants, who accounted for a 10% simple random sample of all health screening participants in 2002 and 2003. The NHIS-HEALS database contained the sociodemographic data of the beneficiaries; medical claims data sets, including diagnoses based on the ICD-10; hospitalization data; medical treatment data based on the Korean Center for Disease Classification and Information–assigned health insurance claims payment codes; and the national health screening data set. The cohort was followed up annually until 2013 for eligibility information including death and health care use. The cohort database was linked to the death registration database of Statistics Korea, which included dates and causes of deaths. As the Korean NHIS enrollment is mandatory for all residents of Korea (16), the health care use information in the NHIS-HEALS database included all visits (inpatient, outpatient, and pharmacy visits) made to health care facilities by cohort subjects (14). The national health screening was performed biennially from 2002 to 2013 and consisted of regular blood tests, chest radiographic examinations, physical examination, and survey questionnaire on medical history. Among the national health screening participants, 31.6% were monitored biennially until 2013 (14), and we used only baseline health screening information as adjustment variables (e.g., BMI and smoking and alcohol habits when enrolled into the cohort). Every sample cohort member had a Korean social security number, which, after constructing of the cohort, was replaced with a serial number to protect personal data. This study received institutional review board approval and was assigned protocol number 4-2017-0218.

Study Cohort

A nationwide population-based cohort study was conducted to include data of subjects newly diagnosed with type 2 diabetes and treated with antidiabetes agents (n = 33,208) from the NHIS-HEALS database. The diagnosis of type 2 diabetes was identified by inpatient or outpatient NHIS claims data with an ICD code for type 2 diabetes (E11). While the follow-up period for this cohort was from 2002 to 2013, we only analyzed data from 2007 to 2013, as DPP-4i were first approved by the Korea Food & Drug Administration in 2007. Pancreatic safety was compared between subjects newly prescribed DPP-4i and those who were newly prescribed other antidiabetes drugs (α-glucosidase inhibitors [αGI], biguanides, meglitinides, sulfonylureas, thiazolidinediones [TZDs], and insulin). The following exclusion criteria were used: *1*) diagnosis of acute or chronic pancreatitis (ICD-10: K85 and K86), either separately or together, or pancreatic cancer (ICD-10: C25) before diagnosis of type 2 diabetes and *2*) a history of GLP-1 receptor agonist use. Finally, data from 33,208 patients were analyzed (Supplementary Fig. 1).

Drug Exposure

The DPP-4i evaluated in the current study included sitagliptin, vildagliptin, linagliptin, saxagliptin, and gemigliptin. Exposure to DPP-4i was lagged by 6 months to account for the latency time and to minimize reverse causality. Considering the uncertainty in the optimal length of the latency time window, sensitivity analyses were conducted by varying the exposure lag period to assess the consistency of results (Supplementary Tables 2 and 3). Drug use was defined as a prescription to antidiabetes drugs based on pharmacy claims data during follow-up. This definition was applied to DPP-4i and other antidiabetes drugs such as αGI, biguanides, meglitinides, sulfonylureas, TZDs, and insulin. Patients with a second prescription for insulin dispensed within 6 months of the initial prescription were defined as insulin users to reflect continuous use rather than temporary use owing to acute medical conditions.

Covariates and Confounding Controls

The outcomes were the incidence of acute or chronic pancreatitis or both and pancreatic cancer in patients newly diagnosed with type 2 diabetes who were being treated with antidiabetes drugs.

Acute pancreatitis and chronic pancreatitis were defined by the registry of ICD codes (ICD-10: K85 and K86) during an admission to the hospital or in an outpatient setting. For calculation of pancreatic cancer incidence, patients admitted to the hospital for pancreatic cancer (ICD-10: C25) were selected using the NHIS inpatient claims data.

Age at the diagnosis of type 2 diabetes was used as a continuous variable or divided into categorical variables (two groups: <65 and ≥ 65 years of age) to investigate differences in the pancreatic safety of DPP-4i across age subgroups. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Smoking status and alcohol intake data were obtained from questionnaires completed during health check-ups. Smoking status was categorized as current and other-than-current smoking. Alcohol intake was divided into daily and other-than-daily alcohol intake. The Charlson Comorbidity Index (CCI) was determined by evaluating and scoring for comorbid conditions (17). The residential region types were classified as rural, urban, or metropolitan. Use of biguanides, sulfonylureas, and TZDs at baseline was considered a confounding factor, as these drugs may modify the risk of developing pancreatitis or pancreatic cancer (18–20). Statistical adjustments were performed using insulin as a time-dependent variable in assessing the hazard ratios (HRs) for pancreatitis or pancreatic cancer to examine exposure-related risks (21,22). A history of gallbladder and common bile duct (CBD) stones was confirmed by the NHIS medical claims data based on ICD codes (ICD-10: K80). Cholecystectomy and gastrectomy data were obtained from the health insurance payroll codes for these procedures. Supplementary Appendix 1 references previous validation studies to support the validity of our database and the codes/algorithms we used to define outcomes, drug exposure, and adjustment variables.

Statistical Analysis

We first compared baseline characteristics based on DPP-4i use using χ^2 tests for categorical variables and *t* tests for continuous variables. We performed analyses using a Cox proportional hazards model with time-dependent covariates to examine whether DPP-4i use was associated with the incidence of pancreatitis or pancreatic cancer. A lag time of 6 months was used to define exposure to DPP-4i. We also obtained results without a lag time in the model. The model was adjusted for age, sex, BMI, smoking status, alcohol intake, CCI, residential region, and use of antidiabetes drugs (biguanides, sulfonylureas, TZDs, and insulin) to investigate the relationship between DPP-4i use and pancreatic safety in patients with type 2 diabetes. In addition, the risk of pancreatitis was adjusted for a history of gallbladder and CBD stones (4,23). The risk of pancreatic cancer was further adjusted for previous cholecystectomy and gastrectomy (24,25). For determination of the heterogeneity of effect size, subgroup analyses were conducted according to age, sex, BMI, smoking status, alcohol intake, CCI, residential regions, and use of antidiabetes drugs (biguanides, sulfonylureas, TZDs, and insulin). The risk of pancreatitis was also analyzed in subgroups according to a medical history of gallbladder and CBD stones. Statistical analyses were performed using the SAS statistical software (version 9.4; SAS Institute, Cary, NC) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Table 1 lists the baseline characteristics of the study subjects. From the NHIS-HEALS database, we identified 33,208 subjects who were newly diagnosed with type 2 diabetes and were newly prescribed antidiabetes drugs from 2007 to 2013; this included 10,218 new users of DPP-4i (DPP-4i users) and 22,990 new users of antidiabetes drugs other than DPP-4i (DPP-4i nonusers). The mean duration of follow-up was 3.60 years for DPP-4i users and 3.35 years for DPP-4i nonusers in the analyses of pancreatitis and 3.63 years for DPP-4i users and 3.42 years for DPP-4i nonusers in the analyses of pancreatic cancer. A total of 1,704 subjects (5.1%) were lost to follow-up owing to disqualification by death or emigration. The overall follow-up rate of our study cohort was 94.9%.

The mean ages of all study subjects, DPP-4i users, and DPP-4i nonusers were 62.1, 60.1, and 62.9 years, respectively. Compared with DPP-4i nonusers, DPP-4i users were younger, with a higher proportion of males. Subjects with obesity and current smokers were more prevalent in DPP-4i users. Meanwhile, subjects who reported daily alcohol intake, had a medical history of gallstones, or had a higher CCI score (≥ 2) were more prevalent in the DPP-4i nonuser group. There were no differences in previous medical histories of cholecystectomy and gastrectomy. Compared with DPP-4i nonusers, more DPP-4i users were from city and metropolitan areas. Insulin use during the follow-up period was not different between DPP-4i users and DPP-4i nonusers. Biguanide and TZD use was more prevalent in DPP-4i users, whereas sulfonylureas use was more prevalent in DPP-4i nonusers.

Safety Against Pancreatitis

Acute and chronic pancreatitis was diagnosed in 869 and 215 subjects, respectively. Of the 1,084 cases of pancreatitis, 156 cases occurred during DPP-4i exposure periods and 928 cases occurred during DPP-4i nonexposure periods (Table 2). The overall incidence rate of pancreatitis was 1,073 and 935 per 100,000 person-years (PYs) in the DPP-4i use and nonuse groups, respectively. Before adjustment for confounding variables, the overall crude risk of pancreatitis in the DPP-4i use group was not statistically significant with or without a 6-month lag period. After adjustment for multiple confounding factors, the risk of pancreatitis was significantly associated with DPP-4i use (aHR 1.27, 95% CI 1.07–1.52; $P = 0.007$). With a 6-month exposure lag for DPP-4i, the aHR for pancreatitis remained statistically significant (aHR 1.24, 95% CI 1.01–1.52; $P = 0.037$).

Older age, male sex, daily alcohol intake, a higher CCI score, and a previous history of gallbladder and CBD stones were significantly associated with an increased risk of pancreatitis (Supplementary Table 1).

To investigate the trends in risks according to the duration of DPP-4i exposure, we performed a Cox proportional hazards model analysis of various time segments since the first DPP-4i prescription (Table 3). The risk of pancreatitis was not significantly affected by exposure duration of DPP-4i. Similar to the results in all cohort subjects, analyses restricted to insulin nonusers revealed no significant trend according to exposure duration.

Table 1—Baseline characteristics of study population

	Total	DPP-4i users	DPP-4i nonusers	P
N	33,208	10,218	22,990	
Sex				<0.001
Male	19,194 (57.8)	6,263 (61.4)	12,925 (56.2)	
Female	14,014 (42.2)	3,947 (38.6)	10,065 (43.8)	
Age (years)†	62.1 ± 9.2	60.1 ± 8.8	62.9 ± 9.3	<0.001
BMI (kg/m^2)†				<0.001
≥25	16,888 (50.9)	5,407 (53.0)	11,478 (49.9)	
<25	16,310 (49.1)	4,799 (47.0)	11,506 (50.1)	
Current smoking†				<0.001
Yes	6,876 (21.4)	2,385 (24.1)	4,491 (20.2)	
No	25,258 (78.6)	7,496 (75.9)	17,762 (79.8)	
Daily alcohol intake†				0.025
Yes	1,821 (5.6)	517 (5.1)	1,304 (5.7)	
No	30,989 (94.4)	9,573 (94.9)	21,416 (94.3)	
Gallbladder and CBD stones				0.024
Yes	910 (2.7)	249 (2.4)	661 (2.9)	
No	32,298 (97.3)	9,969 (97.6)	22,329 (97.1)	
Cholecystectomy				0.856
Yes	166 (0.5)	50 (0.5)	116 (0.5)	
No	33,042 (99.5)	10,168 (99.5)	22,874 (99.5)	
Gastrectomy				0.247
Yes	44 (0.1)	10 (0.1)	34 (0.2)	
No	33,164 (99.9)	10,208 (99.9)	22,956 (99.8)	
CCI score†				<0.001
0	4,428 (13.3)	1,654 (16.2)	2,774 (12.1)	
1	6,836 (20.6)	2,260 (22.1)	4,576 (19.9)	
≥2	21,944 (66.1)	6,304 (61.7)	15,640 (68.0)	
Region†				<0.001
Rural	12,566 (37.8)	3,680 (36.0)	8,886 (38.7)	
City	7,134 (21.5)	2,246 (22.0)	4,888 (21.3)	
Metropolitan	13,508 (40.7)	4,292 (42.0)	9,216 (40.0)	
Insulin use				0.245
Yes	407 (1.2)	136 (1.3)	271 (1.2)	
No	32,801 (98.8)	10,082 (98.7)	22,719 (98.8)	
αGI use†				<0.001
Yes	1,653 (5.0)	434 (4.3)	1,219 (5.3)	
No	31,555 (95.0)	9,784 (95.7)	21,771 (94.7)	
Biguanide use†				<0.001
Yes	23,628 (71.2)	7,648 (74.9)	15,980 (69.5)	
No	9,580 (28.8)	2,570 (25.1)	7,010 (30.5)	
Meglitinide use†				0.296
Yes	560 (1.7)	161 (1.6)	399 (1.7)	
No	32,648 (98.3)	10,057 (98.4)	22,591 (98.3)	
Sulfonylurea use†				<0.001
Yes	13,611 (41.0)	4,042 (39.6)	9,569 (41.6)	
No	19,597 (59.0)	6,176 (60.4)	13,421 (58.4)	
TZD use†				0.030
Yes	1,050 (3.2)	355 (3.5)	695 (3.0)	
No	32,158 (96.8)	9,863 (96.5)	22,295 (97.0)	

Data are presented as number of patients (%) or mean ± SD. †Values at baseline.

Subgroup analyses revealed that the risk of pancreatitis associated with DPP-4i use was not affected by age, sex, or BMI (all interactions showed $P > 0.05$) (Supplementary Fig. 2*A*). In addition, subgroup analysis based on well-documented risk factors of pancreatitis, such as current smoking, daily alcohol intake, a medical history of gallbladder and CBD stones, and a higher CCI score (3,4,23,26), failed to show an interaction between DPP-4i–induced risk of pancreatitis and these confounding factors (all interactions showed $P > 0.05$) There were no significant subgroup differences based on the use of insulin and oral antidiabetes drugs other than DPP-4i (biguanides, sulfonylureas, and TZDs).

Safety Against Pancreatic Cancer

Pancreatic cancer was diagnosed in 237 subjects: 35 cases occurred during DPP-4i exposure periods, and 202 cases occurred during DPP-4i nonexposure periods (Table 2). The incidence rate of pancreatic cancer was 236 and 200 per 100,000 PYs for DPP-4i use and nonuse groups, respectively. Before adjustment for confounding factors, the overall crude HR for pancreatic cancer was not statistically significant (HR 1.32, 95% CI 0.92–1.90; $P = 0.130$). However, statistical significance was obtained for a 6-month exposure lag for DPP-4i (HR 1.55, 95% CI 1.02–2.35; $P = 0.038$). After adjustment for various confounding factors, the risk of pancreatic cancer was significantly higher in the DPP-4i use group than in the nonuse group (aHR 1.50, 95% CI 1.02–2.20; $P = 0.042$). With a 6-month exposure lag, the aHR for pancreatic cancer was still statistically significant (aHR 1.81, 95% CI 1.16–2.82; $P = 0.009$).

Older age and a higher CCI score also had a significantly higher aHR for pancreatic cancer (Supplementary Table 1). Insulin treatment did not show a statistical significance in association with an increased risk of pancreatic cancer (aHR 2.24, 95% CI 0.55–9.08, $P = 0.259$).

Analyses across various time segments since the first prescription of DPP-4i showed that the risk of pancreatitis associated with DPP-4i use was similar in the first 12 months and 1 year after the initial prescription (Table 3). Restricted to insulin nonusers, the effect size for the risk of pancreatic cancer associated with DPP-4i use was generally consistent during the follow-up period as well.

In subgroup analyses, the increased risk of pancreatic cancer associated with DPP-4i use did not show heterogeneity across subgroups according to age, sex, BMI, current smoking, daily alcohol intake, CCI score, residential region, and the use of insulin and oral antidiabetes drugs other than DPP-4i (biguanides, sulfonylureas, and TZD) (Supplementary Fig. 2*B*).

CONCLUSIONS

DPP-4i are widely used antidiabetes medications with clinical benefits. However, the pancreatic safety of DPP-4i use is a rising concern, owing to possible

incretin-based effects or unknown direct effects. In this study, we demonstrated that DPP-4i use was associated with increased risks of both pancreatitis and pancreatic cancer. We analyzed a large nationwide longitudinal data set obtained from the NHIS-HEALS database, which included a total of 33,208 subjects newly diagnosed with type 2 diabetes and prescribed antidiabetes medications and who were followed up from 2007 to 2013.

The clinical relevance of the current study is attributed to several factors. First, we used a sample cohort from a generalized population database comprising individuals with variations in age, comorbidity, and lifestyle. Second, statistical analyses with adjustments for various confounding factors reduced the risk of bias. Third, the risk across various time segments since the first prescription of DPP-4i was analyzed to investigate trends according to exposure duration of DPP-4i. Fourth, subgroup analyses were performed to determine clinical factors that interacted with DPP-4i to increase the risk of pancreatitis and pancreatic cancer. Fifth, we investigated the independent pancreatic safety of DPP-4i, including multiple types of DPP-4i, to confirm class effects.

Several studies have reported significant associations between DPP-4i use and acute pancreatitis (8,13,27,28). Conversely, a large population-based cohort study suggested that the use of incretin-based drugs (GLP-1 receptor agonists and DPP-4i) was not associated with an increased risk of acute pancreatitis compared with other oral antidiabetes drugs (29). Similarly, a retrospective cohort study that evaluated the independent safety of DPP-4i reported that DPP-4i did not significantly increase the risk of acute pancreatitis in older adults (30). In the current study, we observed that DPP-4i use significantly increased the aHR for pancreatitis even after applying an exposure lag of 6 months. The increased risk of pancreatitis associated with DPP-4i use was not heterogeneous according to well-known risk factors for pancreatitis, implying that DPP-4i use could be directly associated with pancreatitis, as this association was not affected by these confounding factors.

The association between pancreatic cancer and DPP-4i use has remained controversial as well. Consistent with a previous study that evaluated the association between incretin-based drugs (GLP-1 receptor agonists and DPP-4i) and pancreatic cancer (31), a number of studies have claimed that DPP-4i alone were not significantly associated with increased pancreatic cancer risk (32,33). In contrast, a cohort study using a public health insurance database showed that incretin-based therapy was associated with an increased risk of pancreatic cancer (aHR 2.14) (7). Moreover, an analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database revealed a potential correlation between DPP-4i use and pancreatic cancer (34). However, the association between DPP-4i and pancreatic cancer has not been extensively investigated. We could study the association between DPP-4i use and pancreatic cancer in a larger number of study subjects based on access to a nationwide cohort database. Similar to the results of subgroup analyses for pancreatitis, the association between DPP-4i use and pancreatic cancer was not affected by other potential confounding risk factors for pancreatic cancer, such as older age, current smoking status, and daily alcohol intake (23). These results indicated that DPP-4i use may have an independent effect on the development of pancreatic cancer.

However, the contribution of reverse causation cannot be excluded in the current study. We found that the risk of pancreatitis and pancreatic cancer did not reveal increasing trend as exposure duration of DPP-4i increased. Furthermore, the effect size for the risk of pancreatitis and pancreatic cancer was not increased as lag time lengthened in the sensitivity analyses (Supplementary Tables 2 and 3). Based on the Korean antidiabetes drug use patterns, DPP-4i use itself could suggest the presence of severe hyperglycemia, which can be an early manifestation of yet undetected pancreatitis and pancreatic cancer (35–37). DPP-4i are recommended as second-line drugs when the initial monotherapy fails to attain glycemic goals and are not typically used as a first-line monotherapy in Korea (38). In contrast, monotherapy prescriptions in Korea comprised 62.5% sulfonylureas and 19.8% metformin in 2007 (38). Furthermore, a 1-year latency period may not be sufficient to assess

Table 2—HRs for pancreatitis and pancreatic cancer associated with DPP-4i use

Exposure group	Events	PYs	Incidence rate*	Crude HR (95% CI)			aHR (95% CI)			
				No time lag	*P*	6-month time lag	*P*	No time lag	*P*	6-month time lag	*P*
Pancreatitis											
DPP-4i use	156	14,545	1,073	1.18 (0.99–1.40)	0.062	1.15 (0.95–1.41)	0.153	1.27 (1.07–1.52)	0.007	1.24 (1.01–1.52)	0.037
Nonuse	928	99,289	935	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Pancreatic cancer											
DPP-4i use	35	14,827	236	1.32 (0.92–1.90)	0.130	1.55 (1.02–2.35)	0.038	1.50 (1.02–2.20)	0.042	1.81 (1.16–2.82)	0.009
Nonuse	202	100,838	200	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	

The aHRs were adjusted for age, sex, BMI, smoking status, alcohol intake, CCI, residential region, and use of antidiabetes drug (biguanides, sulfonylureas, TZDs, and insulin). In addition, the aHR for pancreatitis was adjusted for a history of gallbladder and CBD stones, and the aHR for pancreatic cancer was adjusted for histories of cholecystectomy and gastrectomy. DPP-4i use and insulin use were used as time-dependent covariates. *Per 100,000 PYs.

Table 3—Risks for pancreatitis and pancreatic cancer associated with DPP-4i use by time since the initial prescription

	All subjects				Subjects without insulin use			
DPP-4i exposure category	Events	PYs	Adjusted HR	95% CI	Events	PYs	Adjusted HR	95% CI
Pancreatitis								
No use	928	99,289	1.00 (reference)	—	897	97,829	1.00 (reference)	—
<3 months	33	2,206	1.32	1.00–1.75	31	2,178	1.29	0.96–1.72
3 to <6 months	16	1,875	1.09	0.71–1.66	16	1,852	1.06	0.69–1.65
6 to <12 months	35	3,028	1.39	1.01–1.90	35	2,988	1.43	1.04–1.96
≥12 months	72	7,437	1.19	0.93–1.52	69	7,330	1.18	0.92–1.51
Pancreatic cancer								
No use	202	100,838	1.00 (reference)	—	194	99,307	1.00 (reference)	—
<3 months	7	2,236	1.93	1.17–3.21	7	2,206	1.86	1.10–3.13
3 to <6 months	4	1,900	1.39	0.57–3.42	4	1,876	1.13	0.42–3.08
6 to <12 months	8	3,074	2.00	1.01–3.96	7	3,032	2.04	1.03–4.04
≥12 months	16	7,617	1.95	1.16–3.29	15	7,506	1.86	1.09–3.17

The HRs were adjusted for age, sex, BMI, smoking status, alcohol intake, CCI, residential region, and use of antidiabetes drug (biguanides, sulfonylureas, TZDs, and insulin). In addition, the HR for pancreatitis was adjusted for a history of gallbladder and CBD stones, and the HR for pancreatic cancer was adjusted for histories of cholecystectomy and gastrectomy. DPP-4i use and insulin use were used as time-dependent variables; the reference group was no use of DPP-4i.

development of pancreatic cancer exclusively attributed to DPP-4i. Previously, patients ≥50 years of age with new-onset diabetes showed a six- to eightfold higher risk of pancreatic cancer within 3 years of diagnosis (39). Patients should be observed for at least several years to minimize the potential contribution of reverse causation in assessment of DPP-4i–induced pancreatic cancer risks among patients with newly diagnosed type 2 diabetes. Thus, the association between DPP-4i use and the risk of pancreatitis and pancreatic cancer exclusive of the reverse causality could not be determined in the current study.

Interestingly, the increased risk of pancreatic cancer associated with DPP-4i use did not show a significant interaction with a higher BMI or insulin use, both of which are associated with hyperinsulinemia and pancreatic ductal proliferation (40). As elevated GLP-1 levels induced by DPP-4i use might promote mitogenic signaling in pancreatic ductal cells as well as dysplasia (11), higher BMI and insulin use may act synergistically with increased GLP-1 by DPP-4i to promote pancreatic ductal proliferation. However, mechanisms independent of elevated GLP-1 levels should be considered because endogenous GLP-1 levels increase to within the physiological range in response to DPP-4i (10–25 pmol/L), which is much lower than the pharmacological range achieved in response to GLP-1 receptor agonists (e.g., free active liraglutide levels in the range of 60–90 pmol/L) (41). DPP-4 is a ubiquitously expressed protease and targets diverse peptides to regulate a number of physiological functions (42). For instance, stromal cell–derived factor-1 (SDF-1) is one of the target peptides of DPP-4 (42), and SDF-1/CXCR4 signaling has been reported to induce pancreatic cancer cell invasion and epithelial-mesenchymal transition (43,44). Thus, increased SDF-1 in response to DPP-4i might be a potential candidate that increases the incidence of pancreatic cancer in DPP-4i users. Further studies evaluating the association between DPP-4i and pancreatic cancer independent of GLP-1 are required.

In this study, insulin treatment was not significantly associated with a higher aHR for pancreatic cancer, unlike the results of previous studies (7,22), and did not affect the DPP-4i–induced risk of pancreatic cancer. For interpretation of this result, a low proportion of insulin users due to a specific insulin use pattern in Korea and a limited follow-up duration had to be considered. In Korea, the proportion of insulin users is relatively low compared with that in Western countries (45). In contrast to 29.1% of any insulin users among adult patients with diabetes in the U.S. and up to 39.0% of any insulin users among patients with type 2 diabetes in the European countries (46,47), only 8.9% of patients with any type of diabetes undergo any insulin therapy for glycemic control in Korea (48). Furthermore, we confined our study subjects to patients diagnosed with type 2 diabetes with newly prescribed antidiabetes drugs. According to the Korean Diabetes Association's treatment guidelines for type 2 diabetes, 2017, insulin therapy is recommended after oral combination therapy failure with few exceptions, and insulin is rarely prescribed to patients with newly diagnosed type 2 diabetes in Korea (49). In addition, limited follow-up durations could be another contributing factor for the low proportion of insulin users in the current study, as initiation of insulin treatment was delayed in Korea even for patients with type 2 diabetes uncontrolled by two or more oral hypoglycemic agents (50–52). Hence, insulin use in this study might not adequately reflect the population at a higher risk of pancreatic cancer with severely uncontrolled hyperglycemia and the association between insulin use and the risk of incident pancreatic cancer cannot be determined.

The incidence rates of pancreatitis and pancreatic cancer in our study were higher than those observed in previous studies. Type 2 diabetes has been shown to increase the risk of acute pancreatitis by 2.83-fold, with an incidence rate of 422 per 100,000 PYs (53). For chronic pancreatitis, the incidence rate was estimated to be 200 per 100,000 PYs in the Asia-Pacific region (54). In the current study, the incidence rates of acute and chronic pancreatitis were 760 and 186 per 100,000 PYs, respectively. The incidence rate of pancreatic cancer in a U.S. cohort study was 83.8 per 100,000 PYs among patients with new-onset diabetes (35). In our study, the incidence

rate of pancreatic cancer was 205 per 100,000 PYs in subjects with newly diagnosed type 2 diabetes. The higher incidence of pancreatic disease in our study could be attributed to characteristics of the study subjects. We selected study subjects who were not only newly diagnosed with type 2 diabetes but also taking antihyperglycemic drugs because of poorly controlled hyperglycemia. Poor glycemic control and pancreatitis have been reported to be closely associated (36), and patients with uncontrolled hyperglycemia were much more likely to develop pancreatic cancer than those with well-controlled hyperglycemia (35,37). Furthermore, Asians have a higher risk of developing diabetes-associated pancreatic cancer than people of European and African descent (37). The higher age range in our study (all study subjects $\geq$40 years of age) may have been another contributor to the higher incidence rate of pancreatic disease (23). In addition, we included all cases of pancreatic disease even if it was not the main diagnosis.

The current study has some limitations. First, insufficient information on serum laboratory measurements, such as insulin and triglycerides, could have prevented identification and control of confounding factors. Second, although the NHIS-HEALS database has been validated to have substantial reliability for use in health services research (55–57), the quality of routinely collected national administration data are limited owing to coding errors, incomplete data, medication noncompliance, and limited reliability of self-reporting variables. Third, there may have been cases where pancreatitis or pancreatic cancer was not detected, leading to bias (58). Fourth, subjects with a history of cancer other than pancreatic cancer were not excluded, although ~10% of pancreatic ductal adenocarcinomas have a hereditary component with specific genetic mutations that manifest as several other types of cancers (59). The cohort database in our study did not contain genetic analysis data, increasing the difficulty of determining other cancers that could be genetic risk factors for the development of pancreatic cancer. Fifth, the actual exposure duration of DPP-4i was relatively short, with an average of 1.42 years for subjects with pancreatitis and 1.44 years for subjects with pancreatic cancer. The limited DPP-4i exposure duration could be attributed to the Korean DPP-4i market situation throughout the study period, as the Korea Food & Drug Administration recently authorized marketing of DPP-4i (2007, 2009, 2011, 2011, and 2012 for sitagliptin, vildagliptin, linagliptin, saxagliptin, and gemigliptin, respectively). Further studies with an extended follow-up duration are warranted to confirm long-term pancreatic safety of DPP-4i use.

Collectively, the results of the current study demonstrated that DPP-4i use was associated with increased risks of pancreatitis and pancreatic cancer in patients with newly diagnosed type 2 diabetes. The risk was not affected by potential confounding risk factors. However, considering the absence of trend according to exposure duration of DPP-4i and limited follow-up duration in the current study, the chances of reverse causality cannot be excluded. Therefore, long-term pancreatic safety of DPP-4i has to be further investigated and physicians should develop better strategies to monitor the DPP-4i use in clinical settings, particularly in patients with newly diagnosed type 2 diabetes.

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