EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2023;38:426-435
https://doi.org/10.3803/EnM.2023.1737
pISSN 2093-596X · eISSN 2093-5978

Risk of Pancreatic Cancer and Use of Dipeptidyl Peptidase 4 Inhibitors in Patients with Type 2 Diabetes: A Propensity Score-Matching Analysis

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Background: The effects of dipeptidyl peptidase 4 (DPP-4) inhibitors over the course of long-term treatment remain unclear, and concerns have been raised regarding the role of DPP-4 inhibitors in carcinogenesis in the pancreas. Earlier studies of pancreatic adverse events have reported conflicting results.

Methods: This study analyzed Korean National Health Insurance Service data from January 2009 to December 2012. Patients who had type 2 diabetes mellitus and took two or more oral glucose-lowering drugs (GLDs) were included. Patients prescribed DPP-4 inhibitors (n=51,482) or other GLDs (n=51,482) were matched at a 1:1 ratio using propensity score matching. The risk of pancreatic cancer was calculated using Kaplan-Meier curves and Cox proportional-hazards regression analysis.

Results: During a median follow-up period of 7.95 years, 1,051 new cases of pancreatic cancer were identified. The adjusted hazard ratio (HR) for DPP-4 inhibitor use was 0.99 (95% confidence interval [CI], 0.88 to 1.12) compared with the other GLD group. In an analysis limited to cases diagnosed with pancreatic cancer during hospitalization, the adjusted HR for the use of DPP-4 inhibitors was 1.00 (95% CI, 0.86 to 1.17) compared with patients who took other GLDs. Using the other GLD group as the reference group, no trend was observed for elevated pancreatic cancer risk with increased DPP-4 inhibitor exposure.

Conclusion: In this population-based cohort study, DPP-4 inhibitor use over the course of relatively long-term follow-up showed no significant association with an elevated risk of pancreatic cancer.

Keywords: Pancreatic carcinoma; Dipeptidyl-peptidase IV inhibitors; Diabetes mellitus, type 2

INTRODUCTION

There exists uncertainty regarding the effects of dipeptidyl peptidase 4 (DPP-4) inhibitors over the course of long-term follow-up. Concerns have also been expressed regarding the potential impact of DPP-4 inhibitors on carcinogenesis in the pancreas. Several observational studies and meta-analyses have investigated this issue [1-9], but with mutually inconsistent findings.

Received: 16 May 2023, **Revised:** 29 June 2023, **Accepted:** 3 July 2023

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In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial, saxagliptin use was not associated with significantly increased pancreatic cancer risk compared to placebo. Cancer events and cancer mortality occurred at similar proportions in the saxagliptin and placebo arms during follow-up (median, 2.1 years) [1]. In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study, fewer pancreatic cancer occurred in patients who received sitagliptin than in those who received placebo (9 [0.1%] vs. 14 [0.2%]; hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.28 to 1.51) [2]. However, those results should be interpreted cautiously because those trials had limited durations and reported few events. Furthermore, patients included in randomized controlled trials (RCTs) usually have higher levels of health than patients in the real-world and study cohorts. Furthermore, patients in RCTs are highly selected and reflect only a subset of the real-world population with type 2 diabetes mellitus (T2DM). Similarly, meta-analysis studies that include RCTs are limited by the characteristics of patients in these trials. An observational study showed an association between DPP-4 inhibitors and pancreatic cancer risk (HR, 1.81; 95% CI, 1.16 to 2.82) [3]. A cohort study found that incretin-based therapy had an adjusted HR of 2.14 for pancreatic cancer [4]. However, another observational study showed that DPP-4 inhibitor use was associated with a lower risk of pancreatic cancer than sulfonylurea use (HR, 0.6; 95% CI, 0.4 to 0.6) and exhibited an equivalent risk to that of thiazolidinediones (HR, 1.0; 95% CI, 0.7 to 1.4) [5].

DPP-4 inhibitors first received regulatory approval in Korea in 2007; thus, they have now been in use for more than a decade. Accordingly, their safety in relation to pancreatic cancer can and should be studied in nationwide population-based cohorts with relatively long-term follow-up. This study analyzed data from the Korean National Health Insurance System (KNHIS) database with the aim of determining whether DPP-4 inhibitors are associated with pancreatic cancer risk in patients with T2DM. Since the KNHIS database contains representative data for the entire Korean population, it is suitable for conducting population-based nationwide research on T2DM in Korea.

METHODS

Subjects

A nonprofit organization, the KNHIS is the single insurer responsible for managing Korea's health insurance system. KNHIS subscribers currently comprise approximately 97% of the Korean population, with the remainder being covered through Medical Aid. The Korean National Health Information Database (KNHID) has been extensively used by researchers [10-15] and includes an eligibility database (with information on type of eligibility, socioeconomic status, sex, and age), a medical treatment database (containing data from claims for medical expenses submitted by providers of medical services), a medical checkup database (with data on general health examinations and results from questionnaires about behavioral and lifestyle patterns), a medical care institution database (containing information on the number of physicians, equipment, location, and types of medical institutions), and death information. KNHIS enrollees are recommended to receive health checkups at least biennially [10,11].

The present study included data from 2,748,638 individuals ≥20 years of age who received a national health checkup between January 2009 and December 2012 (index year) and had T2DM. The definition of T2DM was a relevant International Classification of Diseases 10th Revision (ICD-10) code (E11–E14) and a prescription of antidiabetic medications, or a fasting blood glucose (FBG) concentration ≥126 mg/dL measured in the KNHIS health examination [10,11]. We only included patients with T2DM who took two or more oral glucose-lowering drugs (GLDs). A significant number of people either did not take antidiabetic medications after being diagnosed with T2DM or only used monotherapy (n=1,685,221). The reason for limiting the study population to patients taking multiple oral GLDs (n=1,063,214) was that DPP-4 inhibitors are recommended for use as second- to third-line treatments for T2DM [16]. We excluded subjects with any missing values (n=47,328), those with a history of any malignancy before the index year (n=35,278), and those with incident pancreatic cancer during the first year of follow-up (n=7,548) to avoid bias due to reverse causation. The final study population was 973,060 people with T2DM (Fig. 1). Of these, 196,814 used DPP-4 inhibitors and 776,246 used GLDs other than DPP-4 inhibitors. After performing 1:1 propensity score matching (PSM), 51,482 DPP-4 inhibitor users and 51,482 users of other GLDs remained. This study received approval from the Institutional Review Board of The Catholic University of Korea (No. SC22ZISE0176). The requirement for informed consent was waived due to the use of anonymized and deidentified information.

Definition of covariates

Data from the index year were used for the covariates, which included age, sex, socioeconomic status (income level), body mass index (kg/m^2), current smoking status, alcohol consump-

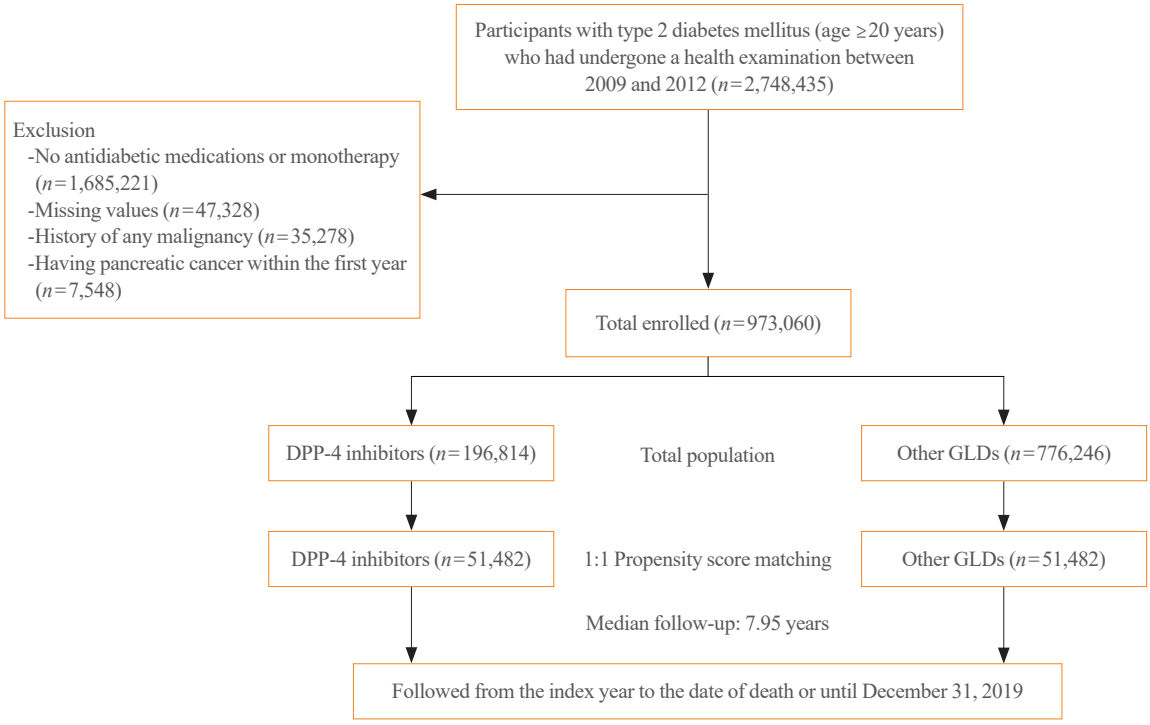

Fig. 1. Study enrollment flow diagram. DPP-4, dipeptidyl peptidase 4; GLD, glucose-lowering drug.

tion (with ≥30 g/day defined as heavy alcohol consumption), exercise (yes/no), and systolic and diastolic blood pressure (mm Hg). The health checkup program in the KNHIS involves anthropometric measurements, laboratory tests, and the administration of detailed lifestyle questionnaires [10,11]. Each participant filled out a self-reported health questionnaire at their health checkup. Blood samples were obtained following overnight fasting, and the serum creatinine, lipid, and FBG levels were quantified.

Oral GLDs were classified as sulfonylureas, metformin, meglitinides, thiazolidinediones, DPP-4 inhibitors, and alpha-glucosidase inhibitors (AGIs). This study did not analyze glucagon-like peptide-1 (GLP-1) receptor agonists because they only became available in Korea after 2015. Prescription information (i.e., the drug class, date prescribed, days of supply, and quantity dispensed) was analyzed.

Definition of primary outcome

Since 2006, the KNHIS has utilized V-codes (i.e., special reimbursement codes) to reduce the copayment rate to 5% for intractable diseases, including cancer. Pancreatic cancer diagnoses must be physician-certified on the basis of clinical data for patients to benefit from this program [10-13]. The ICD-10 code C25 and the reimbursement code for cancer (V193) were used to identify incident pancreatic cancer cases. A sensitivity analysis was conducted that defined pancreatic cancer based on the recording of these two codes during hospitalization.

To analyze the cumulative effect of DPP-4 inhibitors versus other GLDs, the medication possession ratio (MPR) was used [17,18], as defined below:

$$\text{MPR} = \frac{\text{number of days supply obtained during observation period}}{\text{number of days in observation period}} \times 100\ (\%)$$

The time interval (in days) from the index date to the first occurrence of the outcome event was defined as the time to outcome.

Statistical analysis

Categorical and continuous variables were reported as percentages and as mean±standard deviation or median (interquartile range), respectively. The main analyses were carried out after applying PSM to balance potential confounding factors between the groups, with the propensity score for each treatment group calculated via ordinary logistic regression with all the baseline covariates (other than oral GLDs) included in the Cox regression analysis. An acceptable difference in baseline characteristics was defined as an absolute standardized difference (ASD) of no more than 0.1 (10%). The potential effect modification by age (<65 years vs. ≥65 years), sex, use of insulin, number of

Table 1. The Study Population's Baseline Characteristics Pre- and Post-Propensity Score Matching

Characteristic	Overall population			Propensity score-matched population		
	Other GLDs	DPP-4 inhibitors	ASD	Other GLDs	DPP-4 inhibitors	ASD
Number	776,246	196,814		51,482	51,482	
Age, yr	60.78±10.51	57.62±10.68	0.2983	57.86±11.01	58.06±10.84	0.0185
Male sex	434,045 (55.9)	113,719 (57.78)	0.0376	30,181 (58.6)	30,092 (58.5)	0.0035
Smoking status						
Non-smoker	462,638 (59.6)	110,520 (56.2)	0.0699	28,988 (56.3)	28,919 (56.2)	0.0028
Ex-smoker	140,961 (18.2)	40,751 (20.7)	0.0645	10,168 (19.8)	10,255 (19.9)	0.0043
Current smoker	172,647 (22.2)	45,543 (23.1)	0.0215	12,326 (23.9)	12,308 (23.9)	0.0007
Alcohol drinking status						
Non-drinker	500,937 (64.5)	122,269 (62.1)	0.0500	32,157 (62.5)	32,116 (62.4)	0.0017
Mild drinker	213,365 (27.5)	59,228 (30.1)	0.0574	15,225 (29.6)	15,240 (29.6)	0.0007
Heavy drinker	61,944 (8.0)	15,317 (7.8)	0.0074	4,100 (8.0)	4,126 (8.0)	0.0018
Regular exercise	171,201 (22.1)	46,065 (23.4)	0.0325	11,619 (22.6)	11,862 (23.0)	0.0112
Income (lower 25%)	165,106 (21.3)	39,580 (20.1)	0.0286	10,924 (21.2)	10,843 (21.1)	0.0039
BMI, kg/m^2	25.1±3.3	25.2±3.4	0.0074	25.1±3.4	25.1±3.4	0.0036
Waist circumference, cm	86.1±8.4	85.7±8.7	0.0488	85.7±8.6	85.8±8.6	0.0097
FBG, mg/dL	144.1±51.3	139.2±46.4	0.0999	151.6±56.9	148.9±52.8	0.0494
TC, mg/dL	187.7±40.2	177.2±38.6	0.2657	185.4±41.3	183.9±40.7	0.0361
TG, mg/dL	142.1 (141.9–142.3)	133.1 (132.8–133.4)	0.1223	140.2 (139.6–140.9)	139.5 (138.8–140.1)	0.0099
LDL, mg/dL	105.3±39.3	97.7±36.1	0.2003	103.4±40.0	102.4±38.1	0.0242
eGFR, mL/min/1.73 m^2	83.6±35.4	86.4±36.6	0.0770	85.8±34.2	85.6±39.6	0.0058
Systolic BP, mm Hg	128.98±15.6	126.6±15.0	0.1592	127.3±15.4	127.3±15.4	0.0007
Diastolic BP, mm Hg	78.2±9.9	77.4±9.7	0.0746	77.9±9.9	77.8±9.9	0.0061
Duration of diabetes ≥5 yr	483,594 (62.3)	96,919 (49.2)	0.2653	27,903 (54.2)	28,045 (54.5)	0.0056
No. of oral GLDs ≥3	156,190 (20.1)	34,926 (17.8)	0.0605	10,195 (19.8)	11,021 (21.4)	0.0398
Insulin	31,732 (4.09)	2,256 (1.15)	0.1848	2,401 (4.66)	1,424 (2.77)	0.1000
Metformin	682,988 (88.0)	192,478 (97.8)	0.3890	48,018 (93.3)	49,083 (95.3)	0.0894
Sulfonylureas	708,453 (91.3)	36,645 (18.6)	2.1367	42,419 (82.4)	12,209 (23.7)	1.4535
Thiazolidinediones	110,528 (14.2)	1,374 (0.7)	0.5330	9,473 (18.4)	872 (1.7)	0.5787
Alpha-glucosidase inhibitors	188,101 (24.2)	3,057 (1.6)	0.7193	11,210 (21.8)	1,597 (3.1)	0.5899
Meglitinides	21,984 (2.8)	474 (0.2)	0.2118	2,300 (4.5)	264 (0.5)	0.2562

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
GLD, glucose-lowering drug; DPP-4, dipeptidyl peptidase 4; ASD, absolute standardized difference; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; BP, blood pressure.

oral GLDs (<3 and ≥3), diabetes mellitus (DM) duration (<5 and ≥5 years), use of sulfonylureas and the presence of cardiovascular disease or chronic kidney disease were evaluated via stratified analysis and interaction testing with the likelihood ratio test. In our analysis of the total population, pancreatic cancer risk was compared using Kaplan-Meier survival analysis with the log-rank test and multivariable-adjusted Cox hazard regression models based on the study population's baseline characteristics. In the Cox regression analyses, we adjusted for all covariates in Table 1 except for oral GLDs. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical significance was defined using the threshold of a P value <0.05.

RESULTS

Population characteristics

Before PSM, the DPP-4 inhibitor group was younger, had lower FBG and total cholesterol levels, and was less likely to have DM with a duration ≥5 years than the other GLD group. The mean ages of the other GLD and DPP-4 inhibitor groups were 60.8±10.5 and 57.6±10.7 years, respectively. The mean FBG levels of the other GLD and DPP-4 inhibitor groups were 144.1±51.3 and 139.2±46.4 mg/dL, respectively. The proportion of individuals taking three or more oral GLDs was 20.1% in the other GLD group and 17.8% in the DPP-4 inhibitor group.

After 1:1 PSM, a matched cohort with 51,482 DPP-4 inhibitor users and 51,482 other GLD users was generated. Satisfactory balance (ASD <0.10) was found for all clinical characteristics (Table 1). We obtained the distribution of specific GLDs in the other GLD group (sulfonylureas, 82.4%; AGIs, 21.8%; thiazolidinediones, 18.4%; meglitinides, 4.5%). Metformin use was matched in both groups (ASD=0.089).

Risk of pancreatic cancer according to DPP-4 inhibitor use in 51,482 PSM pairs

During follow-up (median, 7.95 years), 1,051 new cases of pancreatic cancer were identified after excluding subjects who de-

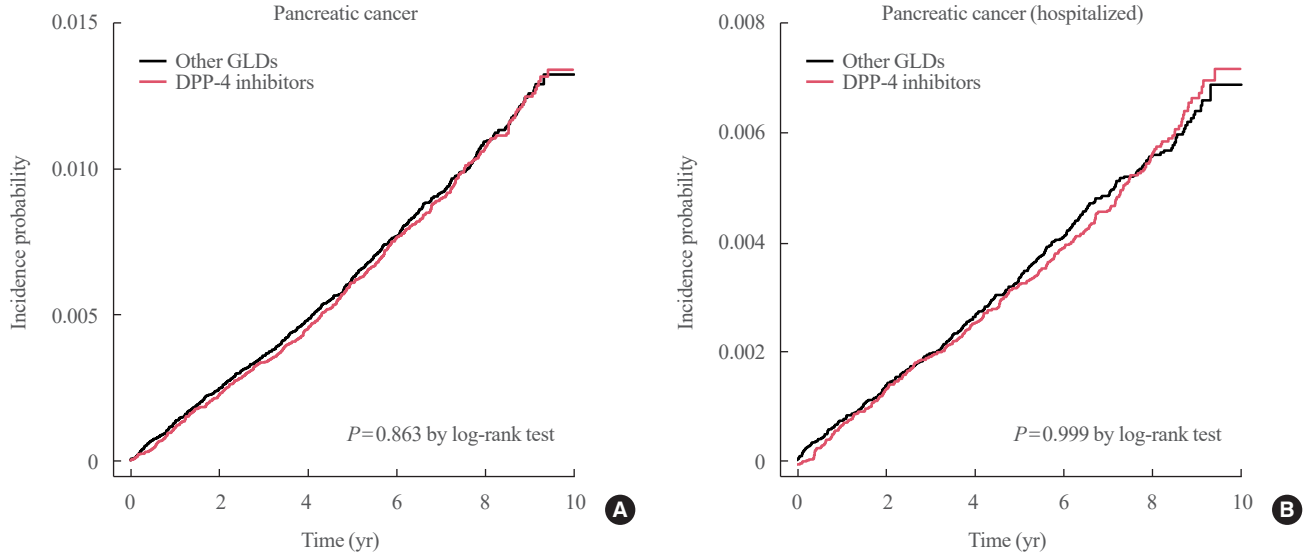

Fig. 2. Kaplan-Meier estimates of the incidence of pancreatic cancer in patients using dipeptidyl peptidase 4 (DPP-4) inhibitors (in red) versus other glucose-lowering drugs (GLDs) (in black). (A) Pancreatic cancer defined by the corresponding International Classification of Diseases 10th Revision (ICD-10) code (C25) and reimbursement V-code for cancer (V193) from the national registration data. (B) Cases diagnosed with pancreatic cancer during hospitalization, defined by the corresponding ICD-10 code (C25) and reimbursement V-code for cancer (V193) from the national registration data.

Table 2. Associations between Dipeptidyl Peptidase 4 Inhibitors versus Other Glucose-Lowering Drugs and Pancreatic Cancer Risk

Variable	Number	No. of events	Incidence rate, /1,000 person-yr	Unadjusted model	Fully adjusted model
Other GLDs	51,482	535	1.356	1 (reference)	-
DPP-4 inhibitors	51,482	516	1.335	0.99 (0.88–1.12)	-
Other GLDs	51,482	535	1.355	1 (reference)	1 (reference)
DPP-4 inhibitors, MPR <50%	14,123	142	1.317	0.97 (0.81–1.17)	1.02 (0.85–1.23)
DPP-4 inhibitors, MPR 50%–79%	9,002	90	1.313	0.97 (0.78–1.21)	1.04 (0.83–1.30)
DPP-4 inhibitors, MPR 80%–99%	21,431	213	1.338	0.99 (0.85–1.17)	0.93 (0.79–1.09)
DPP-4 inhibitors, MPR=100%	6,926	71	1.394	1.04 (0.81–1.33)	0.92 (0.72–1.18)

Values are expressed as hazard ratio (95% confidence interval) for the risk of pancreatic cancer.
GLD, glucose-lowering drug; DPP-4, dipeptidyl peptidase 4; MPR, medication possession rate.

veloped pancreatic cancer during the first year of follow-up. The incidence of pancreatic cancer was not significantly different between the two groups after PSM, demonstrating that DPP-4 inhibitor use showed no association with an elevated risk of pancreatic cancer compared with other GLDs (Fig. 2). The adjusted HR in the DPP-4 inhibitor group was 0.99 (95% CI, 0.88 to 1.12) compared to the other GLD group (Table 2). When the analysis was limited to cases diagnosed with pancreatic cancer during hospitalization, the adjusted HR in the DPP-4 inhibitor group was 1.00 (95% CI, 0.86 to 1.17) compared with the other GLD group (Table 3).

Next, the risk of pancreatic cancer according to patients' adherence to DPP-4 inhibitors was analyzed to assess the cumulative effect of DPP-4 inhibitor exposure on the risk of pancreatic cancer. Among DPP-4 inhibitor users, 55% had an MPR ≥80% and 27% had an MPR <50%. When the other GLD group was used as a reference, a higher MPR for DPP-4 inhibitors was not associated with a higher risk of pancreatic cancer (Tables 2, 3).

Subgroup analysis

The results showed no significant difference in the risk of pancreatic cancer between DPP-4 inhibitors and other GLDs groups across all subgroups (Fig. 3). The same results were seen in all subgroups when the pancreatic cancer diagnosis was confined to hospitalization (data not shown).

Risk of pancreatic cancer according to DPP-4 inhibitor use: total population

In the total study population, in which the median follow-up period was 8.1 years, 10,615 new cases of pancreatic cancer were identified after excluding subjects in whom pancreatic cancer developed during the first year of follow-up. In the overall population, DPP-4 inhibitor use did not show a significant association with a higher risk of pancreatic cancer. After adjusting for all covariates, including baseline characteristics, the adjusted HR was 1.02 (95% CI, 0.93 to 1.12) (Supplemental Table S1). Next, to assess the cumulative effect of drug exposure on the risk of pancreatic cancer, we analyzed pancreatic cancer risk according to patients' adherence to DPP-4 inhibitors. Among DPP-4 inhibitor users, 68% had an MPR ≥80% and 17% had an MPR <50%. Using the other GLD group as a reference group,

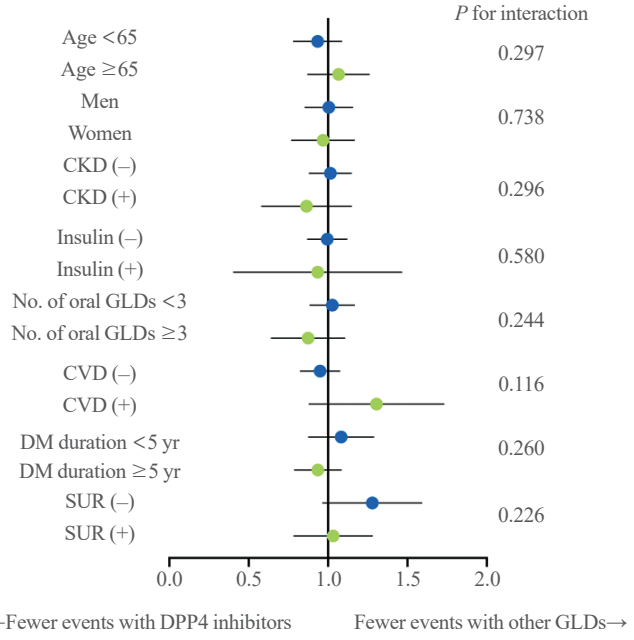

Fig. 3. Subgroup analysis according to baseline characteristics. Hazard ratios and 95% confidence intervals of pancreatic cancer for dipeptidyl peptidase 4 (DPP-4) inhibitors versus other glucose-lowering drugs (GLDs). CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; SUR, sulfonylurea.

Table 3. Associations between Dipeptidyl Peptidase 4 Inhibitors versus Other Glucose-Lowering Drugs and Pancreatic Cancer Risk When the Diagnosis of Pancreatic Cancer Was Defined as during Hospitalization Only

Variable	Number	No. of events	Incidence rate, /1,000 person-yr	Unadjusted model	Fully adjusted model
Other GLDs	51,482	320	0.809	1 (reference)	
DPP-4 inhibitors	51,482	312	0.806	1.00 (0.86–1.17)	
Other GLDs	51,482	320	0.809	1 (reference)	1 (reference)
DPP-4 inhibitors, MPR <50%	14,123	92	0.852	1.05 (0.84–1.33)	1.10 (0.87–1.40)
DPP-4 inhibitors, MPR 50%–79%	9,002	58	0.845	1.05 (0.79–1.39)	1.15 (0.87–1.52)
DPP-4 inhibitors, MPR 80%–99%	21,431	122	0.765	0.95 (0.77–1.17)	0.89 (0.72–1.10)
DPP-4 inhibitors, MPR=100%	6,926	40	0.784	0.99 (0.70–1.35)	0.85 (0.61–1.19)

Values are expressed as hazard ratio (95% confidence interval) for the risk of pancreatic cancer.
GLD, glucose-lowering drug; DPP-4, dipeptidyl peptidase 4; MPR, medication possession rate.

the MPR of DPP-4 inhibitors showed no significant association with pancreatic cancer risk (Supplemental Table S1).

DISCUSSION

DPP-4 inhibitor use did not show a significant association with pancreatic cancer risk in this population-based cohort study. This finding remained consistent when restricting pancreatic cancer diagnoses to hospitalizations and when analyzing the total population before PSM. Moreover, the duration of exposure and adherence to DPP-4 inhibitors were not associated with pancreatic cancer risk. These are important findings regarding the safety of DPP-4 inhibitors, which are the second-most prescribed GLD in South Korea [14].

Meta-analyses of RCTs have not confirmed the possibility of an association between DPP-4 inhibitor use and pancreatic cancer risk. The majority of RCTs included in those meta-analyses measured cancer as a *post hoc* outcome and had a short follow-up duration [1,2,6,7]. In addition, patients in clinical trials are generally healthier than real-world patients, making them less likely to develop cancer than real-world patients. The effects of drugs observed in RCTs often exceed their real-world effectiveness due to lower adherence to medication regimens in real-world patients, as well as the insufficient representativeness of RCT participants. DPP-4 inhibitors first received regulatory approval in Korea in 2007. In this context, observational studies have the advantage of including longer follow-up periods than RCTs, helping them to better capture long-term safety outcomes.

According to a study using a sample cohort from the KNHIS that screened participants between 2007 and 2013, 35 cases were observed during exposure to DPP-4 inhibitors and 202 cases were observed during other anti-diabetes drug exposure [3]. Using a 6-month lag period for drug use, DPP-4 inhibitors were reported to be associated with elevated pancreatic cancer risk (HR, 1.81; 95% CI, 1.16 to 2.82) [3]. The authors pointed out that the possibility of reverse causality could not be ruled out, considering the absence of an increasing trend of pancreatic cancer with exposure duration, and limited follow-up (mean duration of follow-up, 3.6 years). In a previous study [3], only the ICD-10 code C25 was used to diagnose pancreatic cancer, with no use of V-codes. Previous research on the accuracy of ICD codes has concluded that caution should be exercised when interpreting administrative databases that rely solely on ICD codes [19]. The accuracy of using claims submitted for reimbursement purposes to identify patients with cancer is still questionable. Since 2006, the South Korean government has implemented a rare and intractable disease (RID) V-code registration program for 167 diseases, including cancers. Patients can register in the RID program if they are physician-certified as satisfying the diagnostic criteria, and registration makes them eligible for up to a 95% copayment reduction [10,11]. Medical institutions review these records before submission to the KNHIS because the KNHIS can refuse reimbursement if the diagnosis fails to satisfy certain criteria; thus, the diagnoses identified with V-codes have a high degree of reliability [10,11]. A previous study demonstrated the high accuracy of KNHID data gathered using the ICD-10 code and the V-code for pancreatic cancer, with overall sensitivity and specificity values of 99.95% and 98.7%, respectively [20]. Seo et al. [21] found that the overall and age-, sex-, and disease-specific cancer incidence rates were comparable between the KNHIS data and data from the National Cancer Registry of Korea. Their study also emphasized the usefulness of V-codes in the KNHIS database [21]. In our study, we applied both ICD-10 C25 and V-codes to define diagnoses pancreatic cancer. We also performed a sensitivity analysis limited to cases diagnosed during hospitalization. We excluded patients who developed pancreatic disease during the first year of follow-up, and exposure was lagged by 12 months to reduce the potential impact of reverse causality and to account for the latency period. Another advantage of this study is that it included more cases of pancreatic cancer than the above-cited meta-analyses [6,7]. The follow-up period in this study was 8 years, which is relatively long compared to previous studies.

According to a study performed in Belgium and Italy, pancreatic cancer risk doubled shortly after newly prescribed incretin-based therapy [4]. These authors found that the risk of pancreatic cancer in individuals newly prescribed incretin therapy was 3.35 times higher (95% CI, 2.32 to 4.84) in the first three months after the first prescription, and then gradually decreased to 1.69 (95% CI, 1.12 to 2.55) 1 year after the first prescription. Based on the lack of a relationship between the duration of exposure and the risk of pancreatic cancer, the authors concluded that the protopathic bias would adequately explain their findings [4]. Measures of adherence can be used to estimate the cumulative effect of medications. Therefore, we used the MPR to analyze the risk of pancreatic cancer and found no statistically significant relationship. In our study, the incidence of pancreatic cancer per 1,000 person-years (PY) in patients with T2DM was 1.34. When the diagnosis of pancreatic cancer was defined as during hospitalization only, the incidence of pancreatic cancer per 1,000 PY in patients with T2DM was 0.81. This should be taken into account because we only included patients with

T2DM who took two or more GLDs. In another study conducted in Korea, the incidence rate of pancreatic cancer per 1,000 PY in the diabetes group was 1.067, compared with 0.313 in the control, non-diabetic group [22]. Having DM was associated with an increased risk of developing pancreatic cancer (HR, 2.80; 95% CI, 2.31 to 3.40; $P<0.001$) [22]. Although incidence rates are not directly comparable between ethnic groups, Hispanic men and Asians have been reported to have a higher risk of diabetes-associated pancreatic cancer than Caucasians [23].

Metformin use was matched in this study to avoid its associated confounding effects. Over 90% of all subjects were using metformin. In Korea, metformin was the most commonly used GLD (over 80%) during the study period (2009 to 2012), sulfonylureas were the second-most commonly used agents, and DPP-4 inhibitors were the third-most commonly used agents. Metformin use has been reported to have protective effects against colorectal, breast, and pancreatic cancer and is inversely associated with overall cancer morbidity and mortality [24,25]. However, no consensus exists regarding the role of sulfonylurea and insulin use in preventing malignancy, as observational studies have reported inconsistent findings (no association, reduced risk, or increased risk). Notably, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial (median follow-up, 6.2 years) reported no significant association of insulin glargine with overall and cancer-specific outcomes [26]. In our study, the most common comparator oral GLDs were sulfonylureas, followed in descending order by AGIs, thiazolidinediones, and meglitinides (Table 2).

We acknowledge some limitations of this study. First, due to the observational nature of the study, we cannot rule out the possible existence of unmeasured confounders that could not be overcome by PSM. Confounders such as socioeconomic factors or other medical conditions not captured at baseline may have influenced both glucose-lowering medication selection and outcomes. Second, we did not consider patients' history of pancreatitis, but instead adjusted for baseline characteristics such as smoking, alcohol drinking habits, obesity, and hypertriglyceridemia, which are important risk factors for pancreatitis. The diagnosis of pancreatitis through ICD-10 codes is known to be inaccurate in emergency departments and outpatient settings. Recently, GLP-1 receptor agonists and DPP-4 inhibitors have been shown to be associated with an elevated risk of cholecystitis [27,28]. A possible mechanism is that GLP-1 inhibits gallbladder motility and inhibits the secretion of cholecystokinin, which delays gallbladder emptying; alternatively, or that glucose-dependent insulinotropic polypeptide might impact gallbladder relaxation [27]. Because DPP-4 inhibitors are typically prescribed for longer periods of time in routine practice than in clinical trials, it may be particularly important to analyze events related to DPP-4 inhibitors using real-world clinical data. Third, we could not consider the glycemic control status during follow-up, which may be a possible confounder for the incidence of pancreatic cancer. We tried to balance baseline glycemic status by matching FBG levels, number of diabetes medications, and insulin use in comparison groups. Lastly, we could not take into account the duration of DPP-4 inhibitors use before index date. The DPP-4 inhibitors were introduced at the end of 2008 in Korea, then increased dramatically since 2009 [29]. Considering the timing of the introduction of DPP-4 inhibitors in Korea, the difference in duration of use before the index date is estimated to be less than 4 years.

In conclusion, we have collected extensive data on the pancreatic cancer safety of DPP-4 inhibitors over the past decade. In this population-based cohort study with a relatively long follow-up, DPP-4 inhibitor use showed no association with an elevated risk of pancreatic cancer. Newer incretin-based therapies will also need to be studied for safety in terms of pancreatic cancer.

CONFLICTS OF INTEREST

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

ACKNOWLEDGMENTS

This study was supported by Big Data Research Funds from the Korean Society of Endocrinology.

AUTHOR CONTRIBUTIONS

Conception or design: M.K.K., S.J.Y. Acquisition, analysis, or interpretation of data: K.H. Drafting the work or revising: M.K.K., H.S.K. Final approval of the manuscript: M.K.K., S.J.Y.

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