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ORIGINAL RESEARCH

Incident cancer risk in dipeptidyl peptidase-4 inhibitor-treated patients with type 2 diabetes mellitus

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Objective: It is known that patients with diabetes are susceptible to cancer development due to long-standing diabetic conditions. This study aimed to investigate new-onset cancer risk associated with dipeptidyl peptidase-4 (DPP-4) inhibitors as compared to metformin, the first-line antidiabetic agent with promising anticancer activity, in patients with type 2 diabetes mellitus (T2DM).

Methods: A retrospective cohort study of adult T2DM patients was performed at a tertiary care hospital in Korea. Patients who received comparison therapies during 2008–2017 were propensity score (PS)-matched in a 1:1 ratio either to the DPP-4 inhibitors group or to the metformin group in accordance with their primary antidiabetic therapy.

Results: A total of 1538 patients (769 in each group) were found eligible for study entry. Although the rate of newly diagnosed malignancy, irrespective of specific sites or types, was numerically less frequent in the DPP-4 inhibitors group, the difference in overall cancer risk between groups was not statistically significant (HR=1.00, 95% CI=0.56–1.80, *P*=0.998). The PS-matched patients were further stratified by relevant patient factors and diabetes severity. No signal of increased risk of malignant complications among DPP-4 inhibitor-receiving diabetic patients was detected in any of the individual strata, nor in the subgroup patients where insulin-exposed patients were excluded from study analyses in consideration of its carcinogenic properties. Patient death or incident pancreatitis events were seldom encountered in both treatment groups; hence such risks were assessed as negligible with the use of either antidiabetic therapy.

Conclusion: This PS-matched cohort study demonstrated no elevated risk of malignant complications with DPP-4 inhibitor treatment relative to metformin treatment among T2DM patients, irrespective of patient sex, age, comorbid conditions, and diabetes severity status. Similar results were confirmed in the subgroup analyses where a potential confounding effect due to the between-group disparity in insulin co-therapy was eliminated by excluding insulin-exposed patients from risk assessments.

Keywords: cancer, type 2 diabetes, dipeptidyl peptidase-4 inhibitors, metformin

Introduction

Diabetes mellitus, a disease characterized as persistent hyperglycemia, has become a critical health challenge.[1] Individuals diagnosed with diabetes in Asia accounted for more than 200 million of 425 million diabetic patients worldwide in 2017, and the prevalence of the disease increases each year.[2] The rising number of diabetic patients is also an inevitable issue in Korea, where the prevalence of the disease in adults aged ≥30 years was 13.7% (4.8 millions) in 2016.[3,4] Besides, the increased

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rate of childhood obesity has contributed to escalating incidences of type 2 diabetes mellitus (T2DM), a metabolic disorder, in children and adolescents, consequently lowering the age of T2DM diagnosis.[2,5–7]

The emphasis on the proper glycemic control in diabetic patients has grown because of clear correlation between hyperglycemia and the development of diverse complications including nephropathy, neuropathy, retinopathy, and various cardiovascular diseases, such as coronary artery disorders.[8,9] Furthermore, individuals with diabetes have higher incidences of site-specific cancer in bladder, breast, colorectal, endometrial, liver, kidney, and pancreas than non-diabetics,[10–14] which substantially contributed to rising mortality in diabetic patients.

The main treatment modalities of T2DM include lifestyle modifications and pharmacological therapies. Metformin, a biguanide, is the first-line hypoglycemic agent to provide glycemic controls in patients with T2DM or impaired glucose tolerance, otherwise referred to as prediabetes.[1,15] Metformin has been extensively studied for its antineoplastic activities as well as hypoglycemic effects, and a large number of studies confirmed the low risk of malignancy in breast, liver, lung, kidney, ovary, and pancreas with metformin treatment.[10,12,16,17] On the other hand, the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin-based therapy, has been growing steadily over the past decade.[18,19] These agents improve hyperglycemia without the adverse effects associated with older antidiabetic drugs (ADs), such as hypoglycemia, weight gain, chronic heart failure, or edema.[20–24] Notably, however, recent in vitro and in vivo findings suggested that DPP-4 inhibitors may exert pro-metastatic properties when exposed to preexisting cancer cells.[25] AD therapies are life-long, however, as opposed to metformin, the long-term effects of DPP-4 inhibitor use on diabetic complications especially with respect to malignancy development are still in debate and should be clearly established to provide safe patient-centered pharmacotherapy in T2DM patients.

The growing incidences of various site-specific cancer certainly increase morbidity and mortality in T2DM patients. The current treatment guidelines not only recommend age- and sex-appropriate cancer screening but also encourage the reduction of modifiable cancer risks: obesity, physical inactivity, and smoking.[1] Considering declining ages of T2DM diagnosis and increasing life expectancy, the duration of medication usage and the risk for malignant complications are escalating. On the contrary to metformin, the evidence pertaining to the long-term impacts of DPP-4 inhibitors on malignancy is limited. Therefore, the aim of this study is to investigate the risk of incident cancer in T2DM patients treated with DPP-4 inhibitors and perform comparative hazard analyses with metformin to ensure the safety of long-term exposure to DPP-4 inhibitors in T2DM management.

Methods

Study design and cohort

Patient data were collected from electronic medical records (EMRs) of a tertiary care hospital in Korea. Adult patients, aged 18 years or older, with a history of T2DM were identified by the International Classification of Disease, Tenth Revision (ICD-10) codes and screened for study entry if they received either of the two hypoglycemic therapies, DPP-4 inhibitors and metformin, between January 1, 2008 and December 31, 2017. Intraclass switches between DPP-4 inhibitor agents were permitted and collectively categorized as DPP-4 inhibitors use. Study patients were classified into two cohorts of either DPP-4 inhibitors or metformin groups, in accordance with their primary antidiabetic therapy that lasted for at least 6 consecutive months (or 180 days). Those patients treated with both comparison therapies for an equivalent length of time (the number of treatment days not differing by >50% of each other's treatment duration) were excluded from the study, resulting in two mutually exclusive comparison groups. Concomitant therapy with other glucose-lowering medications for diabetes management was allowed. Prespecified exclusion criteria included the following: a cancer diagnosis prior to study entry, age below 18 years, prior dialysis treatment, preexisting end-stage renal disease or renal transplant status at baseline, and any medical history of diabetic coma. To balance potential confounders between treatment groups, eligible patients were then matched in a 1:1 ratio to the DPP-4 inhibitors or metformin groups using propensity score (PS) matching per relevant pretreatment attributes in terms of age, sex, diabetes duration, hemoglobin A1c (HbA1c), and comorbidity status. In consideration of accumulating evidence on insulin's cancer-promoting effects, subgroup analyses were additionally designed, by incorporating only those patients with no exposure to insulin therapy throughout the study period. The 1:1 PS-matching process was repeated for subgroup analyses.

The protocol of this retrospective cohort study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-MDB-18-537). Informed consent from study participants was not required owing to the use of anonymized patient data and the retrospective design of this study. No further ethics approval was necessary because the investigators were authorized by the study institution to analyze patient data for research purposes.

Study outcomes

The primary outcome was the incidence and risk of incident cancer over the follow-up period. The end point event was a composite of newly diagnosed cancer of any types identified by the relevant ICD-10 codes for malignant neoplasms (C00-C97). Individual cancer types were also separately captured along with patient mortality over the study period as secondary end points. Additionally, any hospital encounters associated with incident acute or chronic pancreatitis were identified for safety assessments. The index date for both groups was defined as the first date of initiating the study therapy, either DPP-4 inhibitors or metformin, during the study period. Patient follow-up began on the index date until the earliest occurrence of any of the censoring outcomes as follows: study outcome events, death, follow-up discontinuation, or end of the study period (December 31, 2017), allowing follow-up periods up to 10 years. The outcome date was determined as the earliest date when a patient experienced a given outcome event during the follow-up, but to enhance the reliability and quality of this retrospective database study, only those cases that occurred at least 180 days after the index date were counted as a relevant event and incorporated in risk analyses.

Covariates

Pre-specified covariates included age, sex, tobacco and alcohol use, diabetes duration, HbA1c levels, and comorbidity status at baseline, along with concomitant use of other pharmacologic therapies for glycemic control and for cardiovascular disease management throughout the study period. Diabetes duration in days was determined as the term between the earliest date of T2DM diagnosis as per entire EMRs and the index date in individual patients. In addition to the Charlson Comorbidity Index (CCI) estimated for each patient at baseline, the following pretreatment comorbidities were identified per relevant ICD-10 codes: cardiovascular disease, ischemic stroke, diabetes with chronic complications (exclusive of malignancy-related conditions), COPD, and liver disease. Add-on ADs to the two comparison treatments during the study period were permitted, which include sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, sodium-glucose cotransporter-2 inhibitors, insulin, and glucagon-like peptide-1 agonists. Statins and renin–angiotensin–aldosterone system inhibitors use in study patients was also assessed. Only those patients with treatment duration of at least 30 days by drug class were captured for the assessment of co-medication status.

Statistical analysis

The multinomial PS for individual patients was estimated by fitting a logistic regression model taking into account the aforementioned pretreatment variables as covariates: sex, age category, diabetes duration category, CCI category, HbA1c category, and COPD and liver disease comorbidity at study entry. The PS matching was performed with the caliper matching method to improve the quality of matching due to a great degree of between-group heterogeneity with respect to baseline comorbidities. We calculated incidence rates and HRs along with 95% CIs of end point events by comparing the DPP-4 inhibitors group against the metformin group (reference). The time-to-event in days was determined as the term between the index date and the date of a given outcome event. The PS-matched study patients were further stratified by baseline attributes representing patient factors or disease severity, such as sex (female and male), diabetes duration (<1, 1–4, and ≥5 years), and HbA1c levels (<7%, 7–8%, and ≥9%). Risk analyses were first conducted for incident cancer overall regardless of specific sites or types and then in each stratum by sex, diabetes duration, and HbA1c levels at study entry. A Cox proportional-hazards model was used for the outcome analyses, and a $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of study patients

There were 29,635 patients who had hospital visit episodes associated with T2DM diagnosis over the 10-year study period (Figure 1). Of those, patients who received DPP-4 inhibitors or metformin therapy for at least 6 months with an adherence rate of 80% or greater were captured for an initial cohort. Resultantly, 6201 T2DM patients with

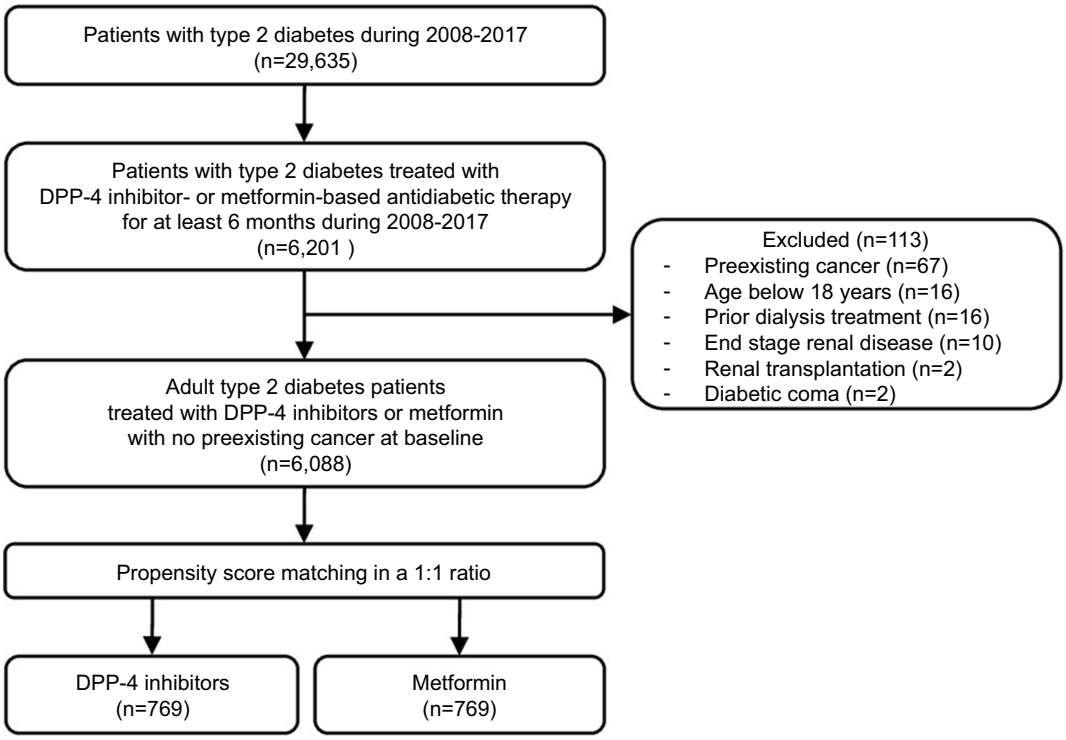

Figure 1 Flow chart for identifying and selecting study patients: T2DM patients with no preexisting cancer, treated with DPP-4 inhibitor- or metformin-based antidiabetic therapy during 2008–2017.
Abbreviations: DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus.

T2DM on either metformin- or DPP-4 inhibitor-based antidiabetic regimens during the study period were screened for study entry. Of those, a total of 113 patients were excluded from further analyses as they met the following exclusion criteria: preexisting cancer (n=67), age below 18 years (n=16), prior dialysis treatment (n=16), end-stage renal disease at baseline (n=10), renal transplant status at baseline (n=2), and history of diabetic coma (n=2). Among the remaining 6088 T2DM patients with no preexisting cancer, 1:1 PS matching was carried out to control for the aforementioned potential confounding variables at pretreatment state. A total of 1538 patients, 769 patients in each group, were then finally selected for study analyses. Table 1 summarizes the baseline characteristics of included patients. No significant between-group differences were observed post-PS matching, with respect to most baseline characteristics, such as age, sex, smoking and drinking history, CCI, diabetes duration, HbA1c, and preexisting comorbidities. The mean HbA1c showed some decrease at the end of follow-up (from 7.8±1.7 to 7.4±1.6 and from 7.8±1.5 to 7.3±1.4 in the DPP-4 inhibitors and metformin groups, respectively), but overall remained stable throughout the study period with no significant difference between groups. The median time under the study medication was approximately 20.6 and 34.3 months in the DPP-4 inhibitors and metformin groups, respectively. The median follow-up duration was approximately 20.4 and 32.9 months in the DPP-4 inhibitors and metformin groups, respectively. The baseline attributes of 6088 patients prior to PS matching are also provided in Supplementary Material Table S1.

Study outcomes

The incidence and risk of new-onset cancer related to DPP-4 inhibitors use as compared to metformin use were assessed in the PS-matched groups (Table 2). The primary outcome event was encountered in 20 (2.6%) and 33 (4.3%) patients in the DPP-4 inhibitors and metformin groups, respectively. Although the rate of newly diagnosed malignancy, regardless of its site or type, was numerically less frequent in the DPP-4 inhibitors group, the difference in overall cancer risk between groups was not associated with statistical significance (HR=1.00, 95% CI=0.56–1.80, P=0.998). To account for differential effects of patient factors as well as the duration and severity of T2DM, the outcome analyses were then stratified into two to three strata by sex, diabetes duration, and HbA1c

Table 1 Baseline characteristics of T2DM patients with no pre-existing malignancy at study entry (1:1 PS-matched DPP-4 inhibitors and metformin cohorts)

	DPP-4 inhibitors n=769	Metformin n=769
Age/years, mean±SD	64.3±12.5	63.5±12.5
18–39, n (%)	16 (2.1)	13 (1.7)
40–64, n (%)	349 (45.4)	334 (43.4)
65–79, n (%)	323 (42.0)	335 (43.6)
≥80, n (%)	81 (10.5)	87 (11.3)
Female, n (%)	333 (43.3)	330 (42.9)
Tobacco, n (%)	236 (30.7)	226 (29.4)
Alcohol, n (%)	222 (28.9)	212 (27.6)
Charlson Comorbidity Index, mean±SD	2.5±1.4	2.3±1.2
≤1, n (%)	251 (32.6)	261 (33.9)
2, n (%)	217 (28.2)	225 (29.3)
≥3, n (%)	301 (39.1)	283 (36.8)
Diabetes duration/days, mean ±SD	1180.3±1714.0	1092.1±1514.8
<1 year, n (%)	428 (55.7)	421 (54.7)
1–4 years, n (%)	141 (18.3)	148 (19.2)
≥5 years, n (%)	200 (26.0)	200 (26.0)
Hemoglobin A1c/%, mean±SD	7.8±1.7	7.8±1.5
<7, n (%)	283 (36.8)	266 (34.6)
7–8, n (%)	330 (42.9)	352 (45.8)
≥9, n (%)	156 (20.3)	151 (19.6)
Comorbidity, n (%)		
Cardiovascular disease	74 (9.6)	52 (6.8)
Ischemic stroke	91 (11.8)	89 (11.6)
Diabetes with chronic complications	313 (40.7)	313 (40.7)
Chronic obstructive pulmonary disease	17 (2.2)	12 (1.6)
Liver disease	74 (9.6)	64 (8.3)
Co-medication, n (%)		
Sulfonylureas	471 (61.2)	442 (57.5)
Thiazolidinediones	73 (9.5)	71 (9.2)
AG inhibitors	13 (1.7)	71 (9.2)
Meglitinides	12 (1.6)	24 (3.1)
SGLT-2 inhibitors	11 (1.4)	38 (4.9)
Insulin	90 (11.7)	132 (17.2)
Statins	503 (65.4)	477 (62.0)
RAAS inhibitors	375 (48.8)	362 (47.1)

Note: No patients were co-medicated with glucagon-like peptide-1agonists for glycemic control.

Abbreviations: PS, propensity score; T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-4; SD, standard deviation; AG, alpha glucosidase; SGLT-2, sodium-glucose co-transporter-2; RAAS, renin–angiotensin–aldosterone system.

levels at baseline, respectively, along with a separate analysis among high-risk patients with preexisting diabetes-related chronic complications. Overall, no signal of increased risk of malignant complications among DPP-4 inhibitor-receiving diabetic patients was detected in any of the individual strata, nor in those high-risk patients. The detailed composition of site-specific cancers was also provided in Table 2; due to the sparsity of each outcome event, the frequency and rate by study groups were only numerically compared without statistical risk analyses. The specific sites that showed the highest, albeit low-level, incidence of new-onset malignancy were breast (6/663, 0.9%), stomach (7/1538, 0.5%), liver (7/1538, 0.5%), and lung (6/1538, 0.4%) in study patients. Patient death or incident pancreatitis events were rarely encountered in both groups; hence such risks were deemed minimal with the use of either glucose-lowering treatment.

Subgroup analyses

In consideration of accumulating evidence on insulin's cancer-promoting properties, subgroup analyses were designed by including only those patients with no insulin exposure throughout the study period, thereby eliminating potential confounding effects owing to the disproportionate distribution of insulin use as co-medication between groups. Patients then underwent an additional 1:1 PS matching that led to a total of 1274 patients (637 in each group) finally selected for subgroup analyses. Risk analyses were repeated in these patients, using the stratification methods analogous to those used for the prior analyses. Table 3 shows the summary results of subgroup analyses. New-onset cancer occurred in 18 (2.8%) and 25 (3.9%) patients in the DPP-4 inhibitors and metformin groups, respectively. Despite the reduced rate of the outcome event with the use of DPP-4 inhibitors, the difference in cancer risk was assessed as statistically insignificant (HR=1.08, 95% CI=0.58–2.03, P=0.81). Similar results were observed when analyses were separately performed in each stratum, irrespective of patient sex, diabetes duration, and HbA1c levels at study entry as well as among those high-risk patients who had preexisting diabetic complications at study entry. Of the various cancer types, breast (5/549, 0.9%), stomach (6/1274, 0.5%), lung (6/1274, 0.5%), and liver (5/1274, 0.4%) were the most common sites of incident cancer, which was consistent with our results from the prior analyses. No signal of increased risk of patient death or incident

Table 2 PS-matched analysis for incidence and relative risk of incident cancer associated with DPP-4 inhibitors versus metformin in T2DM patients

	DPP-4 inhibitors n=769	Metformin n=769	HR	95% CI	*P*-value
Cancer, n (%)	20 (2.6)	33 (4.3)	1.00	0.56–1.80	0.998
Sex, n (%)					
Female	8/333 (2.4)	14/330 (4.2)	1.11	0.43–2.85	0.83
Male	12/436 (2.8)	19/439 (4.3)	0.95	0.45–2.00	0.89
Diabetes duration/years, n (%)					
<1	13/428 (3.0)	12/421 (2.9)	1.43	0.63–3.21	0.39
1–4	1/141 (0.7)	6/148 (4.1)	0.27	0.03–2.35	0.18
≥5	6/200 (3.0)	15/200 (7.5)	0.90	0.33–2.46	0.83
Hemoglobin A1c/%, n (%)					
<7	10/283 (3.5)	10/266 (3.8)	1.30	0.53–3.21	0.57
7–8	10/330 (3.0)	16/352 (4.5)	1.12	0.48–2.60	0.79
≥9	0/156 (0.0)	7/151 (4.6)	NA	NA	NA
Diabetes with chronic complications, n (%)	7/313 (2.2)	18/313 (5.8)	0.82	0.32–2.06	0.66
Cancer types, n (%)					
Esophagus	2 (0.3)	0 (0.0)	NA	NA	NA
Stomach	2 (0.3)	5 (0.7)	NA	NA	NA
Colon	0 (0.0)	3 (0.4)	NA	NA	NA
Rectum	0 (0.0)	2 (0.3)	NA	NA	NA
Liver	3 (0.4)	4 (0.5)	NA	NA	NA
Pancreas	1 (0.1)	2 (0.3)	NA	NA	NA
Other digestive organs	1 (0.1)	1 (0.1)	NA	NA	NA
Lung	0 (0.0)	6 (0.8)	NA	NA	NA
Thymus	1 (0.1)	0 (0.0)	NA	NA	NA
Bone	2 (0.3)	0 (0.0)	NA	NA	NA
Skin	0 (0.0)	1 (0.1)	NA	NA	NA
Breast	3/333 (0.9)	3/330 (0.9)	NA	NA	NA
Ovary	1/333 (0.3)	0/330 (0.0)	NA	NA	NA
Ill-defined and unspecified sites	1 (0.1)	2 (0.3)	NA	NA	NA
Lymphoma	1 (0.1)	2 (0.3)	NA	NA	NA
Multiple myeloma	1 (0.1)	0 (0.0)	NA	NA	NA
Leukemia	1 (0.1)	2 (0.3)	NA	NA	NA
Death, n (%)	1 (0.1)	0 (0.0)	NA	NA	NA
Acute pancreatitis, n (%)	2 (0.3)	1 (0.1)	NA	NA	NA
Chronic pancreatitis, n (%)	1 (0.1)	1 (0.1)	NA	NA	NA

Abbreviations: PS, propensity score; DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus; NA, not applicable.

pancreatitis, both acute and chronic, was detected with the use of either of the two study therapies.

Discussion

A series of clinical studies demonstrated that T2DM patients are at a greater risk of developing malignancy than non-diabetic individuals. In light of growing concerns about malignant complications predisposed by long-standing diabetic conditions, it is important to investigate the potential impact of long-term exposure to ADs on incident cancer development in T2DM patients. DPP-4 inhibitors are one of the most widely used ADs whose prescription volume has grown substantially since their market arrival in the late 2000s,[18,19] but as a relatively new antidiabetic class, their safety track record in terms of incident cancer risk remains relatively limited. Our stratified risk analyses did not find any evidence of increased new-onset malignancy with DPP-4 inhibitor therapy relative to metformin

Table 3 PS-matched subgroup analyses for incidence and relative risk of incident cancer associated with DPP-4 inhibitors versus metformin in T2DM patients never exposed to insulin

	DPP-4 inhibitors n=637	Metformin n=637	HR	95% CI	*P*-value
Cancer, n (%)	18 (2.8)	25 (3.9)	1.08	0.58–2.03	0.81
Sex, n (%)					
Female	7/278 (2.5)	10/271 (3.7)	1.11	0.40–3.10	0.84
Male	11/359 (3.1)	15/366 (4.1)	1.07	0.48–2.37	0.88
Diabetes duration/years, n (%)					
<1	11/369 (3.0)	11/360 (3.1)	1.29	0.54–3.05	0.57
1–4	1/122 (0.8)	5/130 (3.8)	0.37	0.04–3.30	0.33
≥5	6/146 (4.1)	9/147 (6.1)	1.20	0.41–3.54	0.74
Hemoglobin A1c/%, n (%)					
<7	9/250 (3.6)	8/251 (3.2)	1.64	0.61–4.39	0.32
7–8	9/279 (3.2)	13/279 (4.7)	1.06	0.43–2.57	0.90
≥9	0/108 (0.0)	4/107 (3.7)	NA	NA	NA
Diabetes with chronic complications, n (%)	6/240 (2.5)	13/227 (5.7)	0.78	0.28–2.14	0.63
Cancer types, n (%)					
Esophagus	2 (0.3)	0 (0.0)	NA	NA	NA
Stomach	2 (0.3)	4 (0.6)	NA	NA	NA
Colon	0 (0.0)	3 (0.5)	NA	NA	NA
Rectum	0 (0.0)	2 (0.3)	NA	NA	NA
Liver	2 (0.3)	3 (0.5)	NA	NA	NA
Pancreas	1 (0.2)	0 (0.0)	NA	NA	NA
Other digestive organs	1 (0.2)	0 (0.0)	NA	NA	NA
Lung	0 (0.0)	6 (0.9)	NA	NA	NA
Thymus	1 (0.2)	0 (0.0)	NA	NA	NA
Bone	2 (0.3)	0 (0.0)	NA	NA	NA
Breast	3/278 (1.1)	2/271 (0.7)	NA	NA	NA
Ovary	1/278 (0.4)	0/271 (0.0)	NA	NA	NA
Ill-defined and unspecified sites	1 (0.2)	2 (0.3)	NA	NA	NA
Lymphoma	1 (0.2)	1 (0.2)	NA	NA	NA
Leukemia	1 (0.2)	2 (0.3)	NA	NA	NA
Death, n (%)	1 (0.2)	0 (0.0)	NA	NA	NA
Acute pancreatitis, n (%)	2 (0.3)	0 (0.0)	NA	NA	NA
Chronic pancreatitis, n (%)	1 (0.2)	1 (0.2)	NA	NA	NA

Abbreviations: PS, propensity score; DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus; NA, not applicable.

therapy, not only in all strata combined but also separately in each stratum by patient sex, age, diabetes duration, CCI, and HbA1c levels as well as among high risk patients with chronic diabetic complications at baseline. Our subgroup analysis also confirmed such findings, which was designed to verify unconfounded effects of DPP-4 inhibitors versus metformin on incident malignancy, by excluding those with insulin exposure during the study period and thereby eliminating any influence of the agent's cancer-promoting activity. Although drug-induced pancreatitis has previously been associated with DPP-4 inhibitors use, no differential risk of such an adverse event was detected in DPP-4 inhibitors-treated patients as compared to metformin-treated patients in this study.

According to the consensus report published by American Diabetes Association and American Cancer Society in 2010, the disease-specific characteristics of T2DM, such as hyperinsulinemia, insulin resistance, hyperglycemia and fat-induced chronic inflammation act as biological links between diabetes and cancer, increasing

morbidity and mortality in T2DM patients from site-specific malignancies.[1,10] The exact underlying mechanisms of these links are yet to be elucidated; however, hyperinsulinemia and hyperglycemia play pivotal roles in abnormal cell proliferation, anti-apoptosis, and carcinogenesis.[26] Carcinogenetic potentials are initiated by epigenetic changes in oncogenic pathways from chronic hyperglycemia via various molecular mechanisms, promoting the proliferation of abnormal tumor cells.[26] These cells have overexpressed insulin receptor (IR) and/or insulin-like growth factor (IGF) receptor, which generate proliferative signals through phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways.[27] Moreover, tumor cells have increased glucose uptake followed by enhanced glucose metabolism, primarily aerobic glycolysis, which is also referred to as Warburg effect.[10,26] Accordingly, hyperglycemia and subsequent hyperinsulinemia provide favorable environments for tumor cell proliferations in T2DM patients.

Metformin-treated patients were grouped as controls in this study because of the protective activity of metformin against development and proliferation of malignancy, as reported in serial studies.[10,12,17,28,29] Metformin decreases serum glucose by suppressing hepatic glucose production and reducing the gastrointestinal absorption of glucose, and at the same time, enhances the action of insulin in various organs, utilizing excess glucose and consequently decreasing circulating insulin.[30] In addition to breaking the biological links between diabetes and cancer, recognized as hyperglycemia, insulin resistance, and hyperinsulinemia, metformin is suggested to possess antiproliferative effects in tumor cells via various intrinsic cellular metabolisms: ATP synthesis disruption by interruption of mitochondrial oxidative phosphorylation,[31] cell cycle arrest via activation of inhibitory cell cycle factors,[32] growth inhibition by down-regulation of insulin/IGF signaling,[33] and inhibition of Akt/mTOR signaling pathway via adenosine 5′-monophosphate-activated protein kinase (AMPK)-dependent and -independent pathway,[13] and survival restriction in hypoxic environment by suppressing transcription factors.[34]

The use of DPP-4 inhibitor, as opposed to metformin, has been steadily growing since approval of the first DPP-4 inhibiting agent, sitagliptin, by Food and Drug Administration (FDA) in 2006.[18,19,35] Due to short history, the long-term benefits or risks pertaining to DPP-4 inhibitor use are uncertain, providing myriads of conflicting study results. Especially, the impacts of DPP-4 inhibitors on malignancy development are still in debate. The interest in the incident malignancy with DPP-4 inhibitor use received its attention when 223 cases of pancreatic cancer were reported from sitagliptin use in Food and Drug Administration Adverse Event Reporting System (FAERS) from 2007 to 2011.[36] Nonetheless, a large number of studies including meta-analyses revealed no increased risk of site-specific malignancy with DPP-4 inhibitors.[22,37–40] In accordance with the previous results, this study also displayed the evidence of low risk for malignancy with DPP-4 inhibitors in T2DM patients. In fact, albeit statistically insignificant, a tendency toward decreased cancer risk was observed in patients on DPP-4 inhibitors.

Despite a growing body of evidence revealing low risk of incident cancer, DPP-4 inhibitors are not free from suspected malignancy potentials, as noted by controversial findings on DPP-4 inhibitor-induced metastasis.[25] Among the number of debatable mechanisms of metastatic progression, activation of nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor by DPP-4 inhibitors has previously been reported in the animal studies.[25] NRF2 activation provides antioxidant defense in tumor metastatic progression, promoting tumor cell survival under oxidative stress. Nevertheless, the clinical relevance of NRF2 activation with DPP-4 inhibitors in patients with metastatic malignancy is still limited, and recent study results indicated low risk of metastatic activity with DPP-4 inhibitors.[38,41] Consequently, the clinical significance regarding DPP-4 inhibitor-induced metastatic activity should be thoroughly evaluated, and, as of now, DPP-4 inhibitors should be cautiously used in patients with history of malignancy.

The findings from our subgroup analyses, which removed the data related to the patients receiving insulin as co-medication, also confirmed low risk of malignancy in both DPP-4 inhibitor- and metformin-treated patients. Insulin itself is a proliferative factor in malignancy, and exogenous insulin, especially long-acting analogs, has a tendency to increase the risk for malignant complications.[10] Hyperinsulinemia not only activates proliferation signals through overexpressed receptors on the tumor cells but also further increases hepatic IGF-1 production, another signal initiation factor for malignancy progression.[42] Moreover, the metabolic switch to aerobic glycolysis of tumor cells is associated with hyperactivation of IGFR1-IR signaling pathway, primarily induced by elevated circulating insulin and IGF-1 levels rather than genetic

mutations.[43] Thus, close monitoring and appropriate cancer screening are recommended in patients initiating insulin therapy, and further research on preventative and monitoring measures for the exogenous insulin-induced malignancy is required to protect T2DM patients from elevated morbidity and mortality risks.

To the best of our knowledge, this is the first study that assessed the long-term impacts of DPP-4 inhibitors on the risk of incident malignancy in Korea, a country in Asia, where the prevalence of T2DM has increased substantially over the last few decades. The development of malignancy is acknowledged as one of the diabetes complications lately, and long-term impacts of ADs on incident malignancy should be clearly evaluated since these agents are prescribed as life-long treatments and the duration of medication usage is growing secondary to expanded life spans. However, the evidence related to the effects of DPP-4 inhibitors on malignancy is currently lacking with controversial implications. Our study evaluated the incidences of malignancy in patients treated with either DPP-4 inhibitors or metformin using 10-year medical data and revealed low risk of incident malignancy in overall study patients. In addition, this study results suggest that DPP-4 inhibitors have low risk of malignant complications regardless of diabetes duration, HbA1C levels at baseline, and preexisting chronic diabetes-induced complications.

Limitations

As this was a retrospective single-institution study, our findings may not be generalizable to the similar patient population in other clinical settings. Any incorrectly entered or missing information in EMRs regarding diagnostic codes, medication administration, patient characteristics, and laboratory values could have influenced the results of this study. Due to the sparsity of certain outcome events, such as patient death and incident pancreatitis, along with the relatively small sample size, it would not have been possible to detect a potential association between the outcomes and study drug exposure. An assumption was made that all discharge prescriptions were dispensed and that patients completed the full course of treatment as prescribed. Lastly, we were not able to account for any lifestyle modifications and nutritional changes in our assessments, which might have affected health outcomes of study patients; it was assumed that patients on orally administered ADs had at least some dietary intake.

Conclusion

This PS-matched cohort study showed no elevated risk of malignant complications with DPP-4 inhibitor treatment as compared to metformin treatment among T2DM patients, irrespective of patient sex, age, comorbidity status, and diabetes severity. Our subgroup analyses also confirmed similar results, where insulin-exposed patients were excluded from risk assessments in consideration of its carcinogenic properties.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Baseline characteristics of initial cohort T2DM patients with no preexisting malignancy at study entry (prior to PS-matching) (N=6088)

	DPP-4 inhibitors n=902	Metformin n=5,186
Age/years, Mean±SD	64.9±12.8	56.1±12.3
18–39, n (%)	20 (2.2)	461 (8.9)
40–64, n (%)	385 (42.7)	3,353 (64.7)
65–79, n (%)	390 (43.2)	1,262 (24.3)
≥80, n (%)	107 (11.9)	110 (2.1)
Female, n (%)	390 (43.2)	2,205 (42.5)
Tobacco, n (%)	272 (36.9)	1,499 (45.5)
Alcohol, n (%)	264 (36.4)	1,507 (47.3)
Charlson Comorbidity Index, Mean±SD	2.6±1.5	1.9±1.1
≤1, n (%)	296 (32.8)	2,704 (52.1)
2, n (%)	243 (26.9)	1,454 (28.0)
≥3, n (%)	363 (40.2)	1,028 (19.8)
Diabetes duration/days, Mean±SD	1,136.5±1,718.0	799.6±1,318.4
<1 year, n (%)	523 (58.0)	3,307 (63.8)
1-4 years, n (%)	155 (17.2)	929 (17.9)
≥5 years, n (%)	224 (24.8)	950 (18.3)
Hemoglobin A1c/%, Mean±SD	7.7±1.7	7.9±1.7
<7, n (%)	341 (37.8)	1,818 (35.1)
7-8, n (%)	383 (42.5)	2,208 (42.6)
≥9, n (%)	178 (19.7)	1,160 (22.4)
Comorbidity, n (%)		
Cardiovascular disease	85 (9.4)	232 (4.5)
Ischemic stroke	106 (11.8)	386 (7.4)
Diabetes with chronic complications	360 (39.9)	1,331 (25.7)
COPD	24 (2.7)	69 (1.3)
Liver disease	80 (8.9)	611 (11.8)
Co-medication, n (%)		
Sulfonylureas	531 (58.9)	2,655 (51.2)
Thiazolidinediones	78 (8.6)	520 (10.0)
AG inhibitors	16 (1.8)	427 (8.2)
Meglitinides	14 (1.6)	133 (2.6)
SGLT-2 inhibitors	11 (1.2)	346 (6.7)
Insulin	101 (11.2)	764 (14.7)
GLP-1 agonists	0 (0.0)	1 (0.0)

Abbreviations: T2DM, type 2 diabetes mellitus; PS, propensity score; DPP-4, dipeptidyl peptidase-4; AG, alpha glucosidase; SGLT-2, sodium-glucose co-transporter-2; GLP-1, glucagon-like peptide-1.