Association between glucose-lowering treatment and cancer metastasis among patients with preexisting type 2 diabetes and incident malignancy

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Abbreviations: AD: antidiabetic drug; AMPK: adenosine 5'-monophosphate-activated protein kinase; CCI: Charlson Comorbidity Index; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; HIRA: Health Insurance Review and Assessment Service; ICD-10: International Classification of Disease Tenth Revision; mTOR: mammalian target of rapamycin; no-AD: no-antidiabetic drugs; NRF2: nuclear factor erythroid 2 related factor 2; PS: propensity score; ROS: reactive oxygen species.

Novelty and Impact:

Preclinical data suggested that dipeptidyl peptidase-4 (DPP-4) inhibitors may accelerate metastatic progression of preexisting cancer by upregulating the NRF2-driven antioxidant response in cancer cells, which promotes cancer cell survival during oxidative stress. This population-based clinical study found no significant metastatic risk with DPP-4 inhibitors after most types of primary cancer relative to no antidiabetic therapy among diabetic cancer patients except after thyroid cancer, while metastatic risk was decreased with metformin compared with no antidiabetic therapy.

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been suggested to accelerate metastatic progression of preexisting cancer by upregulating the NRF2-driven antioxidant response in cancer cells. DPP-4 inhibitors and other potential NRF2 modulators like metformin are widely used as antidiabetic drugs. However, little is known on how the prognosis of diabetic patients with comorbid cancer differs in terms of metastatic progression across commonly-used glucose-lowering therapies. This population-based clinical

study found no significant metastatic risk with DPP-4 inhibitors after most types of primary cancer compared with no antidiabetic therapy among diabetic cancer patients, except after thyroid cancer, while metastatic risk was decreased with metformin.

ABSTRACT

Preclinical data suggested that dipeptidyl peptidase-4 (DPP-4) inhibitors may promote metastatic progression of preexisting cancer via nuclear factor erythroid 2 related factor 2 (NRF2) activation. We aimed to investigate the association between different glucose-lowering treatments, including DPP-4 inhibitors and metformin, both with potential NRF2 modulating effects, and new-onset metastatic cancer among type 2 diabetes patients with comorbid incident cancer. This population-based cohort study included 223,530 diabetic patients newly diagnosed with primary cancer during 2009-2011 in Korea. The patients were categorized into five study cohorts in accordance with treatment modalities during the follow-up until the end of 2016: no-antidiabetic drugs (no-AD), metformin, DPP-4 inhibitors, metformin+DPP-4 inhibitors, and insulin treatment. Following propensity score (PS) matching in a 1:1 ratio against the no-AD group, 18,805 patients in metformin, 1,865 in DPP-4 inhibitors, 31,074 in metformin+DPP-4 inhibitors, and 1,895 patients in insulin groups were identified for cohort entry and analyzed against the corresponding number of no-AD patients in each PS-matched comparison pair. Metastatic risk was lower with metformin plus or minus DPP-4 inhibitors (HR 0.84, 95% CI 0.79-0.90 and 0.87, 0.80-0.95, respectively), not significantly associated with DPP-4 inhibitors (0.99, 0.77-1.29) except after thyroid cancer (3.89, 1.01-9.64), and higher with insulin therapy (1.81, 1.46-2.24) compared with no-AD use for all cancers combined. In conclusion, DPP-4 inhibitor therapy was not associated with significant risk of cancer metastasis relative to no-AD therapy, irrespective of patient age and sex, except after thyroid cancer, while metastatic risk was decreased with metformin treatment among type 2 diabetes patients with preexisting cancer.

Introduction

Individuals with type 2 diabetes mellitus carry a higher risk of various types of solid and hematologic malignancies than nondiabetic population,[1-4] potentially mediated not only by mutual risk factors and metabolic alterations in the context of elevated plasma glucose levels, insulin resistance and hyperinsulinemia but by adverse effects from prolonged exposure to glucose-lowering therapy.[5-8] Given the rapid rise in diabetes prevalence worldwide and the risk of malignant complications projected to grow among long-term diabetes survivors, prevention of secondary cancer or metastatic spread is of paramount importance in improving the mortality of diabetic patients with comorbid cancer. As these patients are likely to be treated with antidiabetic drugs (ADs) life-long for glycemic control, more research is needed to have a better understanding of the prognostic role of different hypoglycemic treatments in terms of cancer progression.

Among the major glucose-lowering therapies, metformin has been most extensively investigated regarding its direct and indirect antineoplastic properties, and multiple mechanisms of action underlying such activities have been proposed.[9-11] Although preceding meta-analyses yielded conflicting results concerning metformin's antitumor effects for various cancer types,[12-14] a number of epidemiologic studies demonstrated that its use was associated with lower cancer incidence[15-17] and mortality in patients with type 2 diabetes[18,19] relative to insulin treatment which is generally considered to stimulate tumor proliferation by functioning as growth factors.[20] However, little has been known regarding how other oral pharmacologic modalities than metformin may differ in terms of oncologic risk and benefit in diabetic patients. Indeed, a preclinical study lately revealed interesting, albeit still controversial, experimental observations that dipeptidyl peptidase-4 (DPP-4) inhibitors, the most widely

prescribed newer class of ADs, promoted metastatic progression of preexisting cancer in vitro and in vivo, possibly mediated via the activation of nuclear factor erythroid 2 related factor 2 (NRF2) transcription factor.[21] It was proposed that exposure to DPP-4 inhibitors may upregulate the NRF2-driven antioxidant response in cancer cells during oxidative stress, which promotes cancer cell survival during metastasis.[21] No patient-centered clinical trial has yet confirmed such relationship. However, the above findings from experimental animal models may well have a profound impact on comprehensive strategies to improve long-term morbidity and mortality in patients with comorbid type 2 diabetes and cancer, especially those individuals receiving DPP-4 inhibitor therapy in real-world clinical settings.

Thus, opportunities for therapeutic optimization seem huge, such that it is urgently needed to verify the safety of the commonly used ADs in diabetic patients with preexisting cancer. There is a general lack of information on how the prognosis of diabetic patients with comorbid cancer would differ in terms of metastatic progression across commonly-used glucose-lowering therapies in a population-based setting. Therefore, the aim of this study was to investigate the association between different antidiabetic treatment modalities and new-onset metastatic cancer, as compared with no antidiabetic exposure, among diabetic patients with preexisting primary cancer. Secondarily, we evaluated pancreatitis risks associated with different antidiabetic therapies compared against no antidiabetic exposure among diabetic cancer patients.

Materials and Methods

Data source

Patient data were derived from the Korean Health Insurance Review and Assessment Service (HIRA) database, containing administrative data for the entire Korean population of about 50 million beneficiaries that were generated for reimbursement purposes for healthcare services provided under the national health insurance schemes. The HIRA data consist of claims records from all the inpatient and outpatient visits, including patients' demographic attributes, healthcare institution types, medical procedures and services, diagnoses, and medical utilization information including admission dates, length of hospitalization, medical specialty, and prescription records. Diagnoses are coded in accordance with the Korean Standard Classification of Disease Sixth Revision, an adapted version of the International Classification of Disease Tenth Revision (ICD-10). The protocol of this study was approved by the Institutional Review Board of Ajou University (201609-HB-EX-001). Further ethics approval was not required, as the HIRA authorized the authors to analyze anonymized patient data for research purposes.

Study design and cohort

This nationwide population-based study included all adult patients, aged 18 years and older, with a history of primary cancer in Korea, who were identified for the initial study cohort if they had been diagnosed with any type of primary cancer per ICD-10 codes between January 1st 2009 and December 31st 2011. Of those, patients with any record of cancer diagnosis between 2007 and 2008 were excluded, such that we capture only those who were newly diagnosed with primary cancer during the aforementioned patient recruitment period and that we avoid potential effects of anticancer therapy for any prior cancers. The index date for study entry was defined as the date of the first diagnosis of primary cancer in individual patients. In order to ascertain that only those patients with incident cancer and comorbid type 2 diabetes were selected for the study

analysis, subjects were finally deemed suitable for inclusion if they satisfied the pre-specified eligibility criteria as follows: (1) two or more documented type 2 diabetes diagnosis prior to the index date, and (2) no documentation of cancer metastasis prior to study entry or within 180 days post the index date; those patients diagnosed with metastasis within 180 days post study inclusion were excluded from study analyses to improve the quality and reliability of our study findings based on healthcare claims data. Study patients were all required to have continuous hospital records for at least 365 days before and 180 days after the index date. The eligible patients were then categorized into the following five study cohorts in accordance with their treatment modalities during the follow-up period until the end of 2016: no-antidiabetic drugs (no-AD) group (reference), metformin group, DPP-4 inhibitors group, metformin+DPP-4 inhibitors group, and insulin group. Diabetic patients with incident cancer who have not received any prescription for ADs over the study period were classified as the no-AD group. The treatment cohorts of metformin and DPP-4 inhibitors, respectively, were categorized as such if patients were exclusively treated with oral antidiabetic regimens over the follow-up period, primarily based on either metformin or DPP-4 inhibitors but mutually exclusive of each other, with treatment duration of at least 90 consecutive days; co-medication with other oral antidiabetic therapy was permitted, but the two treatment groups were not exposed to each other's therapy. The metformin+DPP-4 inhibitors cohort consisted of those who were on metformin and DPP-4 inhibitor therapy for at least 90 consecutive days respectively but never received any injectable ADs over the study period. Finally, the insulin cohort patients were defined as those receiving insulin for at least 90 consecutive days over the follow-up period regardless of concomitant use of other ADs.

Study outcomes

The primary outcome of interest was the incidence and risk of new-onset metastatic cancer over the study period, as documented according to ICD-10 codes in the HIRA database. All patients were followed up until the occurrence of cancer metastasis, death, or the end of the study period (December 31st 2016), whichever came first, allowing the maximum follow-up period of eight years. In order to identify claims-based evidence of new-onset metastasis, the following algorithm was employed: if patients received a new cancer diagnosis associated with different sites than the primary cancer site per ICD-10 codes at least 180 days post the index date, and (1) the new cancer diagnosis coded on the ensuing claim belonged to C77-80 (secondary neoplasm sites) or (2) the second cancer was classifiable to one of the well-known sites or organs prone to metastasis, including lung, lymph nodes, bone, brain, diaphragm, heart, liver, mediastinum, meninges, peritoneum, pleura, retroperitoneum, and spinal cord.[22] The analyses of metastatic progression in study cohorts were carried out on all primary cancers combined and separately for the common primary cancer sites. Additionally, the incidence and risk of new-onset acute and chronic pancreatitis, occurred at least 180 days post the index date, were tracked and analyzed as secondary safety outcomes.

Covariates

The baseline period was composed of 12 months prior to the index date, during which patient demographic and clinical characteristics, including sex, age, diagnosis data regarding cancer types and dates, diabetes history, and other independent variables such as comorbidities were identified. Patient cohorts were further divided into four age groups: those aged 18-39 years, 40-64 years, 65-79 years, and lastly 80 years or greater. Preexisting comorbidities at study entry were identified per ICD-10 codes and incorporated into study analyses as baseline variables:

hypertension (I10), cardiovascular disease (I21-25), ischemic stroke (I63-64), and microvascular complications, such as nephropathy (E11.2), retinopathy (E11.3), and neuropathy (E11.4). Claims-based evidence of comorbidities was only deemed relevant when individual codes appeared at least twice associated with any visit episodes during the baseline period. Prescription information regarding other glucose-lowering treatments than the study ADs over the study period was also extracted and assessed as co-medication if the respective therapy was continued for at least 90 days. Due to rare use of glucagon-like peptide-1 analogues among study patients, our co-medication assessment was limited to the following five AD categories: sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, and sodium-glucose co-transporter-2 inhibitors.

Statistical analysis

We examined the association between different glucose-lowering therapies in diabetic patients with incident cancer and metastatic progression of the disease, relative to the corresponding comorbid patients but with no exposure to hypoglycemic treatment over the study period (the no-AD group). Patient comorbid conditions were measured by the Charlson Comorbidity Index (CCI). The multinomial propensity score (PS) for each patient was obtained by fitting a logistic regression model incorporating all relevant baseline variables as covariates: age category, sex, primary cancer site, CCI category, comorbidity, and complication status at study entry to perform PS matching between each pair of comparison groups. To address potential confounding, each study cohort was matched against the no-AD group in a 1:1 ratio based on the estimated PS, which predicts the probability of patient exposure to each comparator therapy versus no-AD treatment given the pretreatment variables. To account for the effects of time-varying treatment exposure, the time from the first primary cancer diagnosis till initiation of AD treatment was not classified

as exposed for study analysis. In addition, a supplementary analysis was designed for a head-to-head comparison between DPP-4 inhibitors and metformin with regard to metastatic risk among diabetic cancer patients, with metformin as a new reference treatment. Here, for estimating the PS, we included all the aforementioned baseline covariates plus co-medication history. Patients in the two treatment groups have undergone 1:1 PS matching such that the baseline variables are well balanced. The outcome analyses were performed by using the Cox proportional hazards regression models, and the results were presented with hazard ratios (HRs) and 95% confidence intervals (CIs). The analyses were first performed for primary cancer overall, and then in each stratum by primary cancer site, sex, and age group. All statistical analyses and data management were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The initial study patients eligible for inclusion consisted of 223,530 patients with a history of type 2 diabetes and primary cancer, including those treated with no-AD, metformin, DPP-4 inhibitors, metformin+DPP-4 inhibitors, or insulin therapy during the study period (Figure 1). The mean patient age of initial cohorts prior to PS matching ranged from 61.7 to 63.8 years, and baseline characteristics of those patients were shown in Table S-1 in supplementary material. Each treatment cohort was then matched on the PS in a 1:1 ratio to the no-AD cohort, respectively, for hazard analyses of metastatic progression of primary cancer. Baseline characteristics of PS-matched study patients were presented by individual comparison pairs in Table 1. Overall, there were no significant between-group differences in each pair with respect to age, sex, macro and micro vascular complications of diabetes, and primary cancer sites. Standardized mean difference (SMD) values between PS-matched comparison

groups for each variable were provided in Table S-2. The overall mean duration of follow-up was 5.6±1.8 years, which was comparable across all study cohorts.

Table 2 presents the incidence and hazard of metastatic spread of primary cancer during the follow-up in each PS-matched pair of comparison cohorts. For all cancer sites combined, there existed a general tendency of decreased HRs when metformin was involved as primary therapy in antidiabetic regimens. Compared with no-AD therapy, metformin use with or without DPP-4 inhibitor therapy was associated with lower risk of new-onset metastasis (HR 0.84 with 95% CI 0.79-0.90, and HR 0.87 with 95% CI 0.80-0.95, respectively) in diabetic patients with comorbid cancer. More importantly, unlike the hypothesis suggested in the animal study by Wang et al., DPP-4 inhibitor exposure was not likely to significantly affect the risk of metastatic spread of the disease (HR 0.99 with 95% CI 0.77-1.29). Notably, however, insulin treatment showed statistically significant association with an elevated risk of incident metastasis relative to no-AD use (HR 1.81 with 95% CI 1.46-2.24).

In Figure 2, the differential hazards of developing incident metastatic cancer with 95% CIs and number of cases according to diabetes treatment modalities versus no-AD exposure are graphically summarized via forest plots, subdivided by common primary cancer sites, sex, and age groups. Diabetic patients on metformin regardless of additional DPP-4 inhibitor use had either significantly lower risk or no greater risk of metastatic disease relative to no-AD use during the study period. For specific primary cancer sites, a statistically significant decrease in metastasis risk was observed for prostate cancer in metformin-treated patients, and for liver, prostate, and lung cancer in patients receiving metformin+DPP-4

inhibitors, respectively, compared to those never treated with any ADs. On the contrary, among patients treated with DPP-4 inhibitors alone without metformin exposure, neither protective effects nor hazards were seen for most primary cancer sites except for the single stratum of primary thyroid cancer; the rates and hazards appeared significantly higher with DPP-4 inhibitor use versus no-AD use in diabetic patients with a thyroid cancer history (HR 3.89 with 95% CI 1.04-9.64), albeit with limited clinical relevance due to the low frequency of the outcome event in these patients. With regard to insulin therapy, the hazard analyses showed a general tendency towards increased risks relative to no-AD therapy, with significantly higher HRs (95% CIs) for metastatic progression found in patients after liver, pancreas, and rectum cancer: 1.60 (1.05-2.45), 2.95 (1.32-6.61), and 4.66 (1.28-15.00), respectively.

In subgroup analyses by sex and age groups, distinct patterns were also observed depending on diabetes treatment types (Figure 2). For male, our hazard analysis revealed a general tendency towards decreased HRs with metformin treatment regardless of additional DPP-4 inhibitor therapy, no association with DPP-4 inhibitor-based AD regimens exclusive of metformin, and an upward trend in metastatic cases with insulin treatment, relative to no-AD exposure: the HRs with 95% CIs for cancer overall in males were 0.84 (0.75-0.94) and 0.78 (0.72-0.85) in the metformin and metformin+DPP-4 inhibitors groups respectively, whereas the corresponding HR (95% CI) was 1.63 (1.26-2.10) for insulin users. Interestingly, similar trends were observed for the two age groups of 40-64 years and 65-79 years where most study patients belonged to: the HR (95% CI) of each age group was 0.85 (0.75-0.97) and 0.86 (0.75-0.98) respectively for metformin-treated patients and 0.87 (0.80-0.96) and 0.82 (0.74-0.91) respectively in the metformin+DPP-4 inhibitors group, as opposed to 1.94 (1.41-2.65) and 1.75 (1.28-2.39) respectively for insulin users.

However, in female patients, metastatic risk did not show as distinct patterns as above; neither beneficial nor hazardous effects were observed with metformin- or DPP-4 inhibitors-based therapy in terms of metastatic progression, whereas increased risk was found with insulin therapy as compared to no-AD therapy. Notably, when DPP-4 inhibitors were compared against metformin (new reference) in our supplementary analysis designed for a head-to-head comparison between the two treatments (baseline characteristics post 1:1 PS matching were described in Table S-3, along with SMDs between groups for each variable), the overall risk of metastasis appeared higher with DPP-4 inhibitors relative to metformin (HR 1.34 with 95% CI 1.00-1.78); the hazard analysis just reached statistical significance (P=0.048) (Table S-4). However, no significant risk was observed in most individual strata, irrespective of primary cancer sites and patient sex, except for the single age group of 40-64 years (HR 1.84 with 95% CI 1.19-2.83).

The results of PS-matched hazard analyses regarding the secondary safety endpoints are summarized in Table 3. When individual treatment cohorts were compared against the no-AD cohort, acute pancreatitis risk was reduced with metformin use (HR 0.67 with 95% CI 0.60-0.76) and showed no association with other antidiabetic treatment. Although the incidence rates of acute pancreatitis appeared numerically more frequent in the insulin group versus the no-AD group, no statistically significant differences were noted in its risk between the two treatment groups. Chronic pancreatitis risk was decreased with both metformin- and DPP-4 inhibitors-based therapy (HR 0.73 with 95% CI 0.61-0.87 and HR 0.57 with 95% CI 0.35-0.93, respectively), not significantly associated with metformin+DPP-4 inhibitors therapy, but increased with insulin therapy (HR 1.61 with 95% CI 1.11-2.35), relative to no-AD therapy.

Discussion

Preclinical evidence on dual effects of NFR2-triggered antioxidant defense on cancer growth has been increasingly accumulating lately, which was anticipated to have a substantial impact on cancer management in clinical settings. Previous in vitro and in vivo data demonstrated a paradoxical role of NRF2 in cancer development and progression: NRF2 antioxidant defense system functions as a tumor suppressor in normal cells by preventing reactive oxygen species (ROS)-induced DNA damage, while as an oncogene in malignant cells by promoting cancer cell survival under ROS-rich tumor microenvironment.[23-25] Thus, NRF2 inhibitors could be a promising therapeutic option for the prevention of metastatic progression of preexisting cancer, particularly for those with high NRF2 activity.[26] The controversies surrounding the role of NRF2 in cancer gained further momentum as the previous animal model indicated that some of the widely used ADs may function as NRF2 modulators, such as DPP-4 inhibitors and metformin.[21,23]

In their experimental animal study, Wang and colleagues demonstrated that DPP-4 inhibitors significantly promoted the migration and invasion of cancer in fully malignant cells potentially via activation of the antioxidant response mediated by NRF2 signaling.[21] As revealed in a recent meta-analysis,[27] it is not likely that DPP-4 inhibitors lead to cancer development in nonmalignant tissues because redox responses stimulated by NRF2 activation are a known mechanism of cancer prevention.[28] However, the same cellular defense mechanism could be utilized to fight against chemotherapy and prevent the apoptosis of malignant cells.[23] Given that the DPP-4 inhibitors are recommended by the guidelines as

first- and second-line glucose-lowering therapy and that the number of type 2 diabetes patients receiving DPP-4 inhibitors have been rapidly growing partly due to their favorable safety profile,[29] such association, albeit still controversial, between DPP-4 inhibitors and cancer metastasis promotion may well leave many clinicians worldwide uncertain over the optimal pharmacologic management of diabetic patient populations who are already predisposed to long-term complications of malignant neoplasm.

Notably, the findings in our study suggested elevated risk of metastasis in DPP-4 inhibitor-treated patients with a thyroid cancer history (Figure 2). However, caution is advised in interpreting these findings due to the small sample size with thyroid cancer at baseline and the low frequency of the outcome events in both arms, and thus further study is required to verify such association. Overall, the metastasis-promoting effects of DPP-4 inhibitors suggested in a previous experimental animal study[21] was not confirmed in most primary cancer strata, irrespective of patient age and sex, in this patient-centered clinical outcomes research. Similar results were found in a previous cohort study which showed no higher risk of metastatic spread of preexisting cancer in DPP-4 inhibitor users versus DPP-4 inhibitor never users.[30] Our findings provide additional novel evidence in support of the safety of DPP-4 inhibitors with regard to tumor progression to metastasis in that we defined the control group to be diabetic cancer patients who were never exposed to any type of glucose-lowering therapy over the study period. The control group was prespecified as such with an aim to better understand differential effects of antidiabetic treatment modalities on metastatic progression as compared to no-AD exposure because not only hyperglycemic states but also pharmacologic interventions to control glucose levels are likely to influence the risk of cancer spread in these patients.

To our best knowledge, this is the first study that evaluated the prognostic role of different types of hypoglycemic treatment in terms of cancer metastasis risk using the national healthcare data, accounting for most types of primary cancer and commonly used ADs with NRF2 modulating effects. Our findings suggest that metastatic risk of diabetic cancer patients was lower with metformin-based therapy, not significantly affected by DPP-4 inhibitor therapy, and higher with insulin therapy, relative to no-AD treatment for all cancers combined and for most individual cancer sites. Additionally, with regard to the secondary safety outcomes results, despite the known association between DPP-4 inhibitor exposure and pancreatitis event,[31] no apparent risk was observed with its use as compared to no-AD use.

Another antidiabetic agent that is of special interest due to its unique effects on insulin resistance and hyperinsulinemia is metformin, the guidelines-recommended first-line AD for glycemic control in type 2 diabetes patients, which is also suggested as possessing antiproliferative activity in cancer cells potentially exerted via NRF2-suppressing properties.[23,32] Metformin has been assessed as protective against malignancy development and progression in a series of clinical studies.[15-19,33] Several pathophysiologic mechanisms perhaps underlying its anticancer properties have been proposed: cell-cycle arrest,[10,34] growth inhibition via down-regulation of insulin/insulin-like growth factor (IGF) signaling,[35,36] disruption in mitochondrial respiration,[37] and inhibition of the mammalian target of rapamycin (mTOR) pathway by adenosine 5'-monophosphate-activated protein kinase (AMPK) dependent and independent pathways.[38] Given such evidence, as opposed to DPP-4 inhibitors, it is likely that metformin may reduce the risk of cancer cell proliferation and migration in diabetic patients with preexisting cancer. Consistent

with the notion, this study demonstrated that diabetic patients with preexisting cancer who were exposed to metformin plus or minus DPP-4 inhibitor therapy were at lower risk of experiencing metastatic disease over the study period. These findings could contribute to the repurposing efforts of metformin as anticancer therapy which may also be effective in metastasis prevention for specific groups of patients who have both diabetes and cancer as comorbidities. As suggested by our findings, diabetic cancer patients who require escalation of AD therapy due to diabetes progression or who are already on a DPP-4 inhibitor but not receiving metformin concurrently may benefit from combination therapy based on metformin plus a DPP-4 inhibitor. Although NRF2 related activities of metformin and DPP-4 inhibitors have not been fully elucidated, their potential NRF2 modulating effects as indicated in the prior preclinical study may balance each other out when used in combination, suppressing potential metastasis-promoting effects of DPP-4 inhibitors. Further clinical research with a larger sample size is required to verify such relationship.

In accordance with previous studies, insulin therapy appeared to promote cancer proliferation but likely via a NRF2-independent mechanism. One explanation for such association relates to the hypothesis that exogenous hyperinsulinemia and insulin resistance may accelerate the growth rate and thereby tumor progression.[20] Ranc and others reported that hypoglycemic therapy intensification from non-pharmacologic strategies (diet and lifestyle modifications) towards insulin treatment was significantly associated with higher mortality rates among cancer patients with diabetes than non-diabetic cancer patients.[39] In the present study, metastatic risks were variable with respect to different pharmacologic treatment of diabetes, highest with insulin therapy relative to no antidiabetic medication exposure, exhibiting the HR (95% CI) of 1.81 (1.46-2.24) for all

cancers combined, and similar trends of significantly elevated hazards were observed regardless of sex and in the two largest age groups of 40-64 years and 65-79 years per patient volume. For specific cancer sites, the HRs for metastatic disease also tended to be higher among insulin-treated patients after most cancer types, albeit with marginally significant results in some strata. Not surprisingly, however, metastatic risk post liver, pancreas, and rectum cancers appeared to be substantially affected by insulin therapy as expected with the strong link between hyperinsulinemia and risk of cancer.[40,41] These findings suggest that, although between-group differences in relevant baseline covariates were balanced via PS-matching, it is still possible that the use of more intensive hypoglycemic treatment reflects a greater number of risk factors and more serious complications and comorbidities at the time of study inclusion, and hence poorer prognosis in terms of metastatic progression following primary cancer. Interestingly, we also found that patients treated with insulin had a significant risk increase for chronic pancreatitis. Such association might be attributable to confounding by indication or reverse causality because of the progressive nature of the disease: a larger degree of hyperglycemia, insulin resistance, and beta-cell failure among individuals who were already primarily treated with insulin at study entry.

This study has several limitations inherent to a cohort study using national health insurance data. First, diagnostic cases lacking documentation in claims data could have influenced the frequency of comorbid conditions and end-point events, potentially leading to underestimation of the actual incidence of metastatic cancer. Second, we were not able to obtain laboratory values, such as glycemic control levels, that were not available from the HIRA database. Third, we selected only those patients newly diagnosed with primary cancer during the patient recruitment

period to exclusively include incident cancer cases in our study, but we had no complete and valid information on cancer stage at study inclusion. Although important confounding factors were accounted for by PS matching of comparison cohorts, residual confounding from unknown variables, such as cancer stage and grade at diagnosis, is still possible. Thus, caution is advised in interpreting the study findings. Lastly, an assumption was made that all prescriptions were dispensed and patients finished the entire days' supply, although individual patient compliance can be variable. Nevertheless, the strength of this study is the use of large nationwide dataset that contains the data of all oncologists and entire hospital data in Korea. In clinical research on metastatic progression among cancer patients with preexisting diabetes, sufficient and timely patient recruitment can be a challenge; using the nationwide healthcare database has an advantage when conducting such study. Additionally, the metastatic potential of individual cancers may vary which might be difficult to explore because of the insufficient number of cancer cases when each cancer type is assessed separately. Here, we collectively performed analyses for all cancer types combined and also presented the findings focusing on the most common primary cancer sites prone to metastasis in each comparison pair. Further, the comprehensive information on antidiabetic therapy facilitated evaluation of treatment effects on metastatic risk following incident primary cancer diagnosis. The findings of the present study convey important clinical implications that cancer patients with preexisting diabetes may benefit from novel strategies for therapeutic optimization that takes into consideration metastasis-promoting or -suppressing potentials of glucose-lowering therapy.

In conclusion, this nationwide PS-matched cohort study found no significant risk of cancer metastasis with DPP-4 inhibitor therapy after most types of primary cancer compared with no-AD therapy among diabetic cancer patients, irrespective patient age and sex, except after primary

thyroid cancer. Metastatic risk was decreased with metformin treatment among type 2 diabetes patients with comorbid primary cancer as compared with no antidiabetic therapy.

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Conflicts of Interest

All authors declare no conflict of interest regarding the submitted work.

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Figure Legends

Figure 1. Flow chart of the process of identifying and selecting study patients: type 2 diabetes patients newly diagnosed with primary cancer during 2009-2011.

Abbreviations: ADs: antidiabetic drugs; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; No-AD: no-antidiabetic drugs.

Figure 2. Propensity score-matched hazard analysis for metastasis with different antidiabetic treatments versus no-AD in diabetic cancer patients.

Abbreviations: No-AD: no-antidiabetic drugs; HR: hazard ratio; CI: confidence interval; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors.

Tables

Table 1. Baseline characteristics of type 2 diabetes patients with primary cancer (1:1 propensity score-matched treatment cohorts versus no-AD group)

	Metformin	No-AD	DPP-4 inhibitors	No-AD	Metformin+ DPP-4 inhibitors	No-AD	Insulin	No-AD
	n=18,805	n=18,805	n=1,865	n=1,865	n=31,074	n=31,074	n=1,895	n=1,895
Age/years, n (%)								
18-39	497 (2.6)	524 (2.8)	31 (1.7)	30 (1.6)	880 (2.8)	906 (2.9)	56 (3.0)	56 (3.0)
40-64	9,863 (52.4)	9,907 (52.7)	884 (47.4)	887 (47.6)	17,517 (56.4)	17,531 (56.4)	929 (49.0)	918 (48.4)
65-79	7,426 (39.5)	7,379 (39.2)	839 (45.0)	839 (45.0)	11,655 (37.5)	11,620 (37.4)	805 (42.5)	815 (43.0)
≥80	1,019 (5.4)	995 (5.3)	111 (6.0)	109 (5.8)	1,022 (3.3)	1,017 (3.3)	105 (5.5)	106 (5.6)
Male, n (%)	10,480 (55.7)	10,483 (55.7)	1,139 (61.1)	1,141 (61.2)	18,525 (59.6)	18,565 (59.7)	1,294 (68.3)	1,269 (67.0)
Charlson comorbidity index, n (%)								
≤1	4,107 (21.8)	4,108 (21.8)	338 (18.1)	338 (18.1)	5,113 (16.5)	5,113 (16.5)	51 (2.7)	51 (2.7)
2	4,101 (21.8)	4,090 (21.7)	326 (17.5)	324 (17.4)	5,397 (17.4)	5,395 (17.4)	89 (4.7)	86 (4.5)
≥3	10,597 (56.4)	10,607 (56.4)	1,201 (64.4)	1,203 (64.5)	20,564 (66.2)	20,566 (66.2)	1,755 (92.6)	1,758 (92.8)

Primary cancer site, n (%)								
Stomach	2,351 (12.5)	2,415 (12.8)	258 (13.8)	260 (13.9)	4,093 (13.2)	4,977 (16.0)	202 (10.7)	205 (10.8)
Thyroid	2,449 (13.0)	2,408 (12.8)	146 (7.8)	144 (7.7)	3,220 (10.4)	4,006 (12.9)	69 (3.6)	68 (3.6)
Prostate	2,900 (15.4)	2,843 (15.1)	232 (12.4)	233 (12.5)	4,274 (13.8)	4,225 (13.6)	163 (8.6)	166 (8.8)
Liver	2,237 (11.9)	2,268 (12.1)	315 (16.9)	314 (16.8)	4,338 (14.0)	3,883 (12.5)	568 (30.0)	558 (29.4)
Colon	1,617 (8.6)	1,542 (8.2)	165 (8.8)	174 (9.3)	2,907 (9.4)	2,498 (8.0)	142 (7.5)	156 (8.2)
Lung	1,227 (6.5)	1,195 (6.4)	103 (5.5)	103 (5.5)	1,949 (6.3)	2,256 (7.3)	139 (7.3)	127 (6.7)
Breast	970 (5.2)	968 (5.1)	80 (4.3)	73 (3.9)	1,459 (4.7)	1,295 (4.2)	31 (1.6)	51 (2.7)
Rectum	557 (3.0)	517 (2.7)	55 (2.9)	43 (2.3)	972 (3.1)	840 (2.7)	32 (1.7)	39 (2.1)
Bladder	459 (2.4)	470 (2.5)	59 (3.2)	48 (2.6)	781 (2.5)	805 (2.6)	57 (3.0)	47 (2.5)
Kidney	240 (1.3)	349 (1.9)	72 (3.9)	69 (3.7)	548 (1.8)	607 (2.0)	43 (2.3)	42 (2.2)
Cervix uteri	309 (1.6)	286 (1.5)	35 (1.9)	31 (1.7)	474 (1.5)	428 (1.4)	17 (0.9)	18 (0.9)
Pancreas	640 (3.4)	614 (3.3)	65 (3.5)	52 (2.8)	1,493 (4.8)	693 (2.2)	128 (6.8)	117 (6.2)
Comorbidity, n (%)								
Hypertension	10,509 (55.9)	10,450 (55.6)	1,128 (60.5)	1,127 (60.4)	17,448 (56.2)	17,416 (56.1)	1,284 (67.8)	1,254 (66.2)
CVD	2,290 (12.2)	2,522 (13.4)	255 (13.7)	293 (15.7)	3,775 (12.2)	4,294 (13.8)	377 (20.0)	387 (20.4)
Ischemic Stroke	1,161 (6.2)	1,151 (6.1)	132 (7.1)	133 (7.1)	1,944 (6.3)	1,933 (6.2)	218 (11.5)	202 (10.7)
Microvascular complication, n (%)								
Nephropathy	295 (1.6)	505 (2.7)	153 (8.2)	111 (6.0)	312 (1.0)	515 (1.7)	435 (23.0)	330 (17.4)
Neuropathy	1,071 (5.7)	818 (4.3)	155 (8.3)	154 (8.3)	1,104 (3.6)	822 (2.7)	532 (28.1)	478 (25.2)
Retinopathy	100 (0.5)	103 (0.5)	26 (1.4)	15 (0.8)	123 (0.4)	104 (0.3)	140 (7.4)	52 (2.7)
Co-medication, n (%)								
Sulfonylureas	7,556 (40.2)		1,000 (53.6)		21,678 (69.8)		578 (30.5)	
Thiazolidinediones	1,553 (8.3)		276 (14.8)		6,337 (20.4)		106 (5.6)	
AG inhibitors	1,694 (9.0)		231 (12.4)		6,486 (20.9)		419 (22.1)	
Meglitinides	308 (1.6)		154 (8.3)		1,639 (5.3)		300 (15.8)	
SGLT-2 inhibitors	413 (2.2)		17 (0.9)		990 (3.2)		4 (0.2)	

Abbreviations: No-AD: no-antidiabetic drugs; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; CVD: cardiovascular disease; AG inhibitors: α-glucosidase inhibitors; SGLT-2 inhibitors: sodium-glucose co-transporter-2 inhibitors.

Table 2. Propensity score-matched analysis for incidence and risk of metastasis associated with different antidiabetic treatments versus no-AD in diabetic cancer patients

	Metformin vs. No-AD		DPP-4 inhibitors vs. No-AD		Metformin+DPP-4 inhibitors vs. No-AD		Insulin vs. No-AD	
Incidence of metastasis, n (%)	906 (4.8)	1,148 (6.1)	103 (5.5)	130 (7.0)	1,607 (5.2)	1,940 (6.2)	218 (11.5)	137 (7.2)
HR (95% CI)	0.87 (0.80-0.95)		0.99 (0.77-1.29)		0.84 (0.79-0.90)		1.81 (1.46-2.24)	
P-value	0.003		0.97		<0.001		<0.001	

Hazard ratios were calculated using the time dependent Cox proportional-hazards model.
Abbreviations: No-AD: no-antidiabetic drugs; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; HR: hazard ratio; CI: confidence interval.

Table 3. Propensity score-matched analysis for incidence and risk of acute or chronic pancreatitis associated with different antidiabetic treatments versus no-AD in diabetic cancer patients

	Metformin vs. No-AD		DPP-4 inhibitors vs. No-AD		Metformin+DPP-4 inhibitors vs. No-AD		Insulin vs. No-AD	
Incidence of acute pancreatitis, n (%)	443 (2.4)	891 (4.7)	56 (3.0)	129 (6.9)	1,382 (4.4)	1,449 (4.7)	105 (5.5)	100 (5.3)
Acute pancreatitis, HR (95% CI)	0.67 (0.60-0.76)		0.96 (0.68-1.34)		1.03 (0.95-1.11)		1.29 (0.97-1.70)	
P-value	<0.001		0.80		0.46		0.08	
Incidence of chronic pancreatitis, n (%)	202 (1.1)	369 (2.0)	23 (1.2)	67 (3.6)	593 (1.9)	659 (2.1)	65 (3.4)	49 (2.6)
Chronic pancreatitis, HR (95% CI)	0.73 (0.61-0.87)		0.57 (0.35-0.93)		0.96 (0.86-1.08)		1.61 (1.11-2.35)	
P-value	<0.001		0.02		0.52		0.01	

Hazard ratios were calculated using the time dependent Cox proportional-hazards model.
Abbreviations: No-AD: no-antidiabetic drugs; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; HR: hazard ratio; CI: confidence interval.