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DPP4i, thiazolidinediones, or insulin and risks of cancer in patients with type 2 diabetes mellitus on metformin–sulfonylurea dual therapy with inadequate control

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ABSTRACT

Introduction This study aims to compare the risks of cancer among patients with type 2 diabetes mellitus (T2DM) on metformin–sulfonylurea dual therapy intensified with dipeptidyl peptidase 4 inhibitors (DPP4i), thiazolidinediones, or insulin.

Research design and methods We assembled a retrospective cohort data of 20 577 patients who were free of cancer and on metformin–sulfonylurea dual therapy, and whose drug treatments were intensified with DPP4i (n=9957), insulin (n=7760), or thiazolidinediones (n=2860) from January 2006 to December 2017. Propensity-score weighting was used to balance out baseline covariates across the three groups. HRs for any types of cancer, cancer mortality, and all-cause mortality were assessed using Cox proportional-hazards models.

Results Over a mean follow-up period of 34 months with 58 539 person-years, cumulative incidences of cancer, cancer mortality, and all-cause mortality were 0.028, 0.009, and 0.072, respectively. Patients intensified with insulin had the highest incidence of all-cause mortality (incidence rate=3.22/100 person-years) and the insulin itself posed the greatest risk (HR 2.46, 95% CI 2.25 to 2.70, p<0.001; 2.44, 95% CI 2.23 to 2.67) compared with thiazolidinediones and DPP4i, respectively. Comparing between thiazolidinediones and DPP4i, thiazolidinediones was associated with higher risk of cancer (HR 1.43, 95% CI 1.25 to 1.63) but not cancer mortality (HR 1.21, 95% CI 0.92 to 1.58) and all-cause mortality (HR 0.99, 95% CI 0.88 to 1.11). Insulin was associated with the greatest risk of cancer mortality (HR 1.36, 95% CI 1.09 to 1.71; 1.65, 95% CI 1.31 to 2.07) compared with thiazolidinediones and DPP4i, respectively.

Conclusions For patients with T2DM on metformin–sulfonylurea dual therapy, the addition of DPP4i was the third-line medication least likely to be associated with cancer mortality and cancer effect among three options, and posed no increased risk for all-cause mortality when compared with thiazolidinediones.

Significance of this study

What is already known about this subject?

- There is a consistent increase in site-specific cancer incidences among patients with type 2 diabetes mellitus.
- For those unable to achieve optimal glycemic control after 3 months of metformin–sulfonylurea dual therapy, intensification with third-line glucose-lowering medications is considered as part of the stepwise approach.
- No previous studies examined the effects of insulin, dipeptidyl peptidase 4 inhibitors (DPP4i), and thiazolidinediones (TZD), as third-line glucose-lowering medications, on risk of overall cancer and specific tumor sites.

What are the new findings?

- Insulin as a third-line medication was found to have the highest incidence of cancer mortality and all-cause mortality.
- Basal insulin was shown to be associated with further reduction in all-cause mortality compared with other insulin regimens with overall higher dose.
- TZD as third-line medication was found to have the highest incidence and risk of cancer events, but of insignificant differences in risks of cancer mortality and all-cause mortality in comparison with insulin.

How might these results change the focus of research or clinical practice?

- For patients on metformin–sulfonylurea with inadequate control, DPP4i was the third-line option least likely to be associated with cancer mortality and cancer effect among three options.

BACKGROUND

Both diabetes and cancer pose enormous disease burden worldwide, in which the incidence of cancer has been increased partly due to rising trend of diabetes.[1] A number of large-scale epidemiological studies and meta-analyses showed a consistent increase in site-specific cancer incidences among patients with type 2 diabetes mellitus (T2DM).[2]

Metformin–sulfonylurea (Met-SU) is a common pharmacological treatment for the management of diabetes. For those unable to achieve optimal glycemic control after 3 months of Met-SU dual therapy, intensification with third-line glucose-lowering medications is considered as part of the stepwise approach. The consensus report published by American Diabetes Association and the European Association for the Study of Diabetes in 2018 and reinstatement in 2019 advocated the use of thiazolidinediones (TZD) following Met-SU therapy when cost is a major issue for patients without existing cardiovascular disease.[3 4] So far, a few studies have assessed the associated cancer risk of dipeptidyl peptidase 4 inhibitor (DPP4i), insulin, and TZD due to possible physiological mechanisms.[5–12] There are systematic reviews indicating that DPP4i does not increase the risks of cancers or site-specific cancers; however, the immunomodulatory functions of DPP4i increase the glucagon-like peptide-1 levels and may be associated with an increased risk of cancer.[5 7 13] Besides, the relatively short follow-up duration of the included studies (mostly ranged from 52 weeks to 3 years) in these systematic reviews resulted in the uncertainties in long-term cancer risks associated with DPP4i.[5 7] The physiological processes by which endogenous insulin increases levels of circulating insulin elevating risks of cancer are understood, whereas TZD as insulin sensitizer decreases insulin resistance exerting anti-cancer effects.[14] Indeed, there are evidences suggesting that initiating insulin therapy for over 1 year significantly increased the colorectal cancer risks among patients with T2DM with an adjusted HR of 2.1, while TZD could significantly reduce the overall incidence risks of cancers, especially bowel and breast cancers.[9 12] Based on the pooled evidences, few studies quantified and compared the risks of cancers among insulin, TZD, and DPP4i users, let alone measuring their associated cancer risks as third-line medications through a common modulation of treatment with Met-SU dual therapy.

Given the lack of those clinical evidence, it is vital to investigate the associated cancer risks of DPP4i, insulin, and TZD, specifically pioglitazone. Alongside, heterogeneity of patients is likely to be present in previous analyses with pooling of patients on first-line, second-line, or third-line glucose-lowering medications. In this respect, a large-sample population-based analysis has been conducted to examine the effects of insulin, DPP4i, and TZD, as third-line glucose-lowering medications, on risk of overall cancer and specific tumor sites.

RESEARCH DESIGN AND METHODS

Data source description

We assembled the population-based retrospective cohort from the Hong Kong Hospital Authority (HA) administrative database in the Hong Kong adult diabetes population from January 1, 2006 to December 31, 2017. HA database has been extensively used for conducting high-quality large population-based studies.[15 16] Documented DM diagnosis was defined as the International Classification of Primary Care, Version 2 (ICPC-2) codes T89/T90 or International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification (ICD-9-CM) codes 250.x. The database contains comprehensive individual patient-level information on prescription and dispensing of glucose-lowering medication, serial readings of anthropometric and laboratory variables including body weight, body mass index (BMI), waist circumstance, HbA1c, systolic (SBP) and diastolic blood pressure (DBP), total cholesterol levels, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), serum creatinine, fasting glucose and triglycerides, and presence of comorbidities as classified based on the ICD-9-CM or ICPC-2 diagnosis codes.

Our HA drug prescription database contains information on all glucose-lowering medication prescriptions dispensed in pharmacy departments managed under HA during the observation period. For each drug prescription, information including the date of drug dispensing, dosage unit, and quantity of drug dispensed is recorded. We included patients who received dual therapy of metformin and SU between January 2006 and December 2017 and was intensified with one of the following glucose-lowering medications: DPP4i, insulin, or TZD. Patients who were under 18 years old, type 1 DM, had no DM diagnosis code, occurred cancer events before the third-line medication initiation, received first glucose-lowering medication before 2007 (to allow 1-year screening period), received other glucose-lowering medications within 180 days after third-line medications initiation, and received other glucose-lowering medication drug classes before metformin and SU were commenced, were excluded. Baseline date of eligible patients was defined as the date of initiating third-line medication. Patients were observed from the baseline date until the incidence of event outcome, death from any cause, and censored at the last healthcare service utilization date, whichever came first.

Outcome measures

Our study outcomes were time to the risk of cancer of the lip, oral cavity, and pharynx, digestive organs (including esophagus, stomach, small intestine, colon, rectum, anus, liver, gallbladder and extrahepatic bile duct, and pancreas), respiratory system, bone, skin and soft tissue, breast and genital organs, urinary organs, eye, brain and central nervous system, endocrine glands and lymphatic and hematopoietic tissue cancer mortality, and all-cause mortality.[17] Cancer events were identified by the diagnosis codes of the ICD-9-CM and the ICPC-2. Cause of death was defined by 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes. Patients with codes of C00–C97 were those who died from cancers. All the ICD-9-CM, ICD-10, and ICPC-2 diagnosis codes for comorbidities and event outcomes are listed in online supplementary table 1.

Baseline covariates

The baseline covariates included age, gender, and clinical characteristics such as body weight, BMI, waist circumstance, HbA1c, SBP, DBP, total cholesterol levels, LDL-C, HDL-C, serum creatinine, fasting glucose and triglycerides, Charlson Comorbidity Index (CCI), and duration of DM drug use before intensification with third-line medication (ie, the time between the first glucose-lowering medication and the first third-line medication prescription).

Statistical analysis

Patients were grouped according to their third-line medications. Baseline characteristics were described as mean and SD for continuous variables, frequency, and proportion for categorical variables.

To minimize the outcome bias due to discrepancy in baseline covariates, inverse probability of treatment weights (IPTW) using the propensity score was applied to balance covariates across the three groups. Multinomial logistics regression model was performed to calculate the propensity scores of each patient and included the baseline covariates as mentioned previously in the model. Duration of patient on Met-SU dual therapy was calculated to account for person-time exposed to metformin and SU in each group. The IPTW using the propensity scores was implemented using a STATA command marginal mean weighting through stratification.[18] The lowest and highest 1% propensity-score weights in each group were removed to trim extreme weights. In the context of IPTW, the multiple imputations (see below) followed by pooling treatment effects estimates across imputed datasets is the preferred approach.[19] After the propensity-score weighting, the balance of baseline covariates between the groups was further assessed using the absolute standardized mean difference (ASMD). All maximum pairwise ASMDs that were less than 0.2 implied optimal balance between the groups.[20]

To address missing baseline data, multiple imputations by chained equations (MICE) were used for three treatment groups. BMI, HbA1c, SBP, DBP, LDL-C, total cholesterol, HDL-C, serum creatinine, triglyceride, and fasting glucose were imputed by other parameters such as gender, age, duration between first-line medication and third-line medication, and CCI.[21] Model parameters were estimated from multiple imputed data and then used to obtain multiple-imputation linear predictions by applying Rubin's combination rules observation wise to the completed-data predictions.[21] Propensity-score weighting was applied using the predictions obtained after MICE, where five imputed datasets were created for multiple imputations.[22 23]

Incidence rates (IRs) of each outcome event for each group were estimated using the total number of patients with event occurrence during the follow-up period divided by person-years at risk. Cox proportional-hazards regression model was used to examine the association between the third-line medications and incidence of events. HR and its 95% CI were reported for each treatment group in the regression model. Log-rank test was used to compare the equality of the survival curves between the groups. Predictive accuracy of Cox models was assessed and compared using Harrell's discrimination C-index, ranging from zero to one. A value of 0.5 indicates no predictive discrimination, and values of 0 or 1.0 indicate perfect separation of patients. Proportional-hazards assumptions were confirmed through Schoenfeld residuals test. Goodness-of-fit of Cox regression model was assessed using Akaike information criterion and Bayesian information criterion.

Sensitivity analysis was conducted to include pioglitazone only in TZD drug class, and excluded rosiglitazone as it had already been taken off the market in many countries. Likewise, the effects in lowering the risks of outcome events for basal insulin (Neutral Protamine Hagedorn insulin and long-acting insulin) users were assessed in a sensitivity analysis. The complete-case analysis and competing risk for mortality were accounted for the analysis of cancer events in sensitivity analyses. We calculated the E-values as a sensitivity analysis to quantify the potential for unmeasured confounding bias on observed treatment–outcome association.[24 25] The E-value is the minimum strength of association required between an unmeasured confounder and treatment, and between confounder and outcome, conditional on measured covariates, to negate the observed treatment–outcome association.[24 25] E-values for each outcome were calculated using an online calculator.[26] Also, we included patients who received Met-SU dual therapy but were not treated with third-line medications to compare the incidences of cancers, cancer mortality, and all-cause mortality with those who received third-line medications. Patients who were under 18 years old, did not have T2DM diagnosis code, had previous cancer diagnosis, or had first dispensing date before 2007 were excluded. Patients were further divided into two groups based on their baseline HbA1c (<7% and ≥7%).

All statistical analyses were performed using STATA V.13.0 (StataCorp LP, College Station, Texas). All significance tests were two-tailed and p values <0.05 were taken to indicate statistical significance.

RESULTS

The selection process of the cohort group is outlined in the flowchart in figure 1. In total, 20 577 eligible patients were included in current analysis. Among all, majority of patients received DPP4i (48.4%) as their third-line medication, followed by insulin (37.7%) and TZD (13.9%).

Patient characteristics

Table 1 illustrates the baseline characteristics of patients according to their treatment groups before and after weighting. All maximum pairwise ASMDs of characteristics were less than 0.2, implying that all covariates achieved a balance across the three groups. Details of

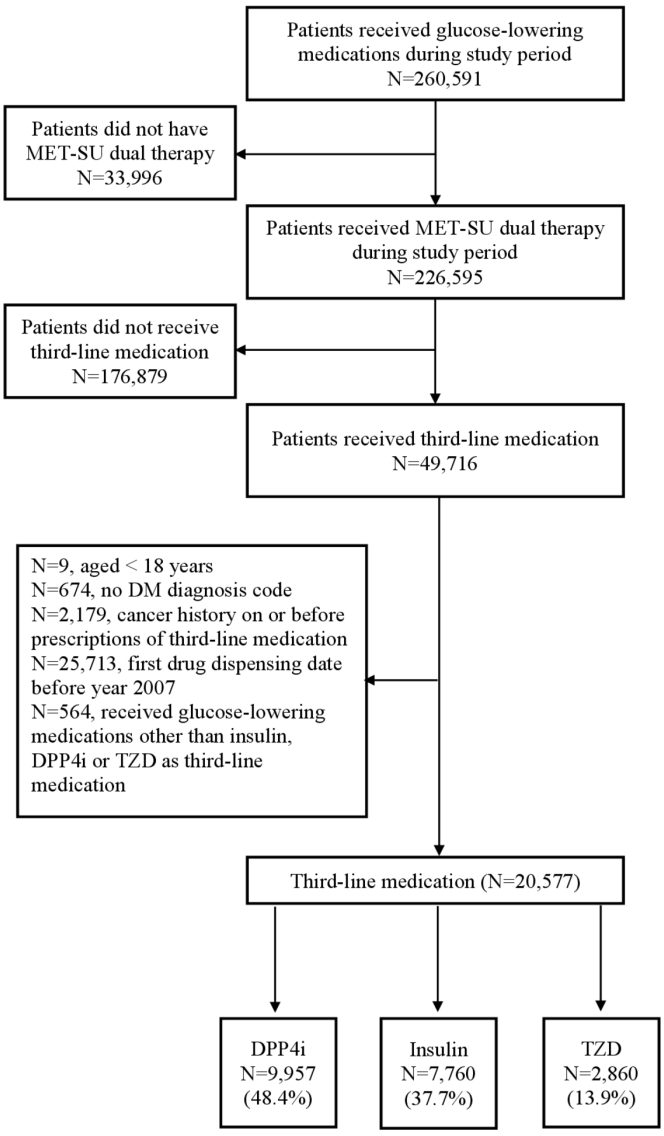

Figure 1 Enrollment of patients who had inadequate control with metformin–sulfonylurea dual therapy and received DPP4i, insulin, or TZD as third-line medications. DM, diabetes mellitus; DPP4i, dipeptidyl peptidase 4 inhibitor; MET-SU, metfomin-sulfonylurea; TZD, thiazolidinediones.

baseline characteristics in each group after weighting are listed in online supplementary table 2.

Incidence rates

Table 2 depicts the cumulative incidence and IRs of cancer, cancer mortality, and all-cause mortality across the follow-up period for patients treated with insulin, DPP4i, and TZD as part of the triple therapy. Over a mean follow-up period of 34 months with 58,539 person-years, cumulative IRs of cancer, cancer mortality, and all-cause mortality were 0.028, 0.009, and 0.072, respectively. The mean follow-up period of our cohort ranged from 34 to 35 months across outcome events, whereby TZD users were only followed up for a shorter period of 19 months.

Patients on TZD had the most incidence of cancer events (IR=1.27/100 person-years), with cancers mainly occurring in the digestive system, respiratory system, and urinary organs. On the other hand, patients intensified with insulin had the most incidences of cancer mortality (IR=0.37/100 person-years) and all-cause mortality (IR=3.22/100 person-years) on propensity-score weighting.

Risk of cancer, cancer mortality, and all-cause mortality

Table 3 and figure 2 compare the HRs of cancer, cancer mortality, and all-cause mortality across three treatment groups. In terms of risk of overall cancer events, its risk of TZD compared against DPP4i was the highest and of statistical significance (HR 1.43, 95% CI 1.25 to 1.63, p<0.001). With regard to cancer events on specific sites, TZD was associated with the greatest risks of cancers in the urinary organs (HR 2.30, 95% CI 1.46 to 3.62, p<0.001). Insulin was associated with the highest risk of pancreatic cancer (HR 3.97, 95% CI 2.00 to 7.88, p<0.001) against TZD. The risk of cancer mortality of insulin against DPP4i was the highest with nearly 1.6-fold increase (HR 1.65, 95% CI 1.31 to 2.07, p<0.001) in its risk followed by insulin versus TZD (HR 1.36, 95% CI 1.09 to 1.71, p=0.007). In contrast, the risk of all-cause mortality of insulin against TZD was the highest among groups with approximately 2.5-fold relative increase (HR 2.46, 95% CI 2.25 to 2.70, p<0.001) in its risk. This relative risk difference was followed by insulin versus DPP4i (HR 2.44, 95% CI 2.23 to 2.67, p<0.001).

Sensitivity analysis

Results of sensitivity analyses were in line with those in the main analysis. When those who received rosiglitazone were excluded in the sensitivity analysis, it became evident that pioglitazone was associated with higher risk in all-cause mortality (HR 1.13, 95% CI 1.00 to 1.27, p=0.044) when compared with DPP4i. The relative risk difference of cancer mortality of pioglitazone versus DPP4i remained comparable with that of TZD group, similar to that of the risk of overall cancer events of pioglitazone (HR 1.31, 95% CI 1.14 to 1.50, p<0.001). The risk of cancer in the urinary organs remained the highest and of statistical significance (HR 2.31, 95% CI 1.40 to 3.80, p=0.001). Basal insulin demonstrated consistent reduction in risk of all-cause mortality relative to TZD (HR 1.78, 95% CI 1.63 to 1.95, p<0.001) and DPP4i (HR 1.58, 95% CI 1.45 to 1.72, p<0.001).

When analysis was conducted to account for competing risk of death, TZD had the highest risk of overall cancer event risk compared with DPP4i (HR 1.46, 95% CI 1.28 to 1.65, p<0.001). The risk of pancreatic cancer of insulin versus TZD remained the highest and of statistical significance (HR 3.80, 95% CI 1.82 to 7.91, p<0.001).

Results of sensitivity analyses were in line with those in the main analysis. Insulin was associated with the highest risks of all-cause mortality and cancer mortality compared with DPP4i and TZD. On the other hand, TZD was associated with the highest risk of cancer events, particularly in the urinary organs, whereas insulin was associated with the highest risk of pancreatic cancer.

Table 1 Baseline characteristics of patients intensifying with DPP4i, insulin, or TZD as third-line medication

	Total	DPP4i	Insulin	TZD	Maximum pairwise ASMD	
					Before weighting	After weighting
General information						
Total no of participants	20 577	9957	7760	2860		
Age (years), mean±SD	59.98±11.97	60.37±11.31	60.15±13.18	58.15±10.47	0.261*	0.049
Gender, n (%)					0.362*	0.176
Female	9015 (43.81%)	4317 (43.36%)	3435 (44.27%)	1263 (44.16%)		
Male	11 562 (56.19%)	5640 (56.64%)	4325 (55.73%)	1597 (55.84%)		
Clinical parameter						
Laboratory result, mean±SD						
HbA1c, %	8.69±1.63	8.48±1.26	9.10±2.05	8.30±1.21	0.146	0.024
SBP, mm Hg	133.45±16.89	133.72±16.45	134.29±18.04	130.21±14.70	0.222*	0.091
DBP, mm Hg	76.81±9.98	76.99±10.02	76.70±10.30	76.50±8.89	0.082	0.030
LDL-C, mmol/L	2.39±0.78	2.38±0.75	2.47±0.85	2.24±0.69	0.150	0.057
HDL-C, mmol/L	1.12±0.29	1.12±0.27	1.13±0.31	1.12±0.26	0.043	0.048
BMI, kg/m^2	28.46±4.03	28.60±4.00	28.17±4.06	28.75±4.01	0.205*	0.107
Waist, cm	96.37±20.15	96.39±15.98	96.27±22.98	96.54±24.82	0.120	0.072
TC, mmol/L	4.34±0.96	4.32±0.90	4.44±1.06	4.15±0.86	0.266*	0.073
Triglyceride, mmol/L	1.88±1.30	1.87±1.24	1.92±1.39	1.79±1.19	0.228*	0.098
Creatinine (serum), µmol/L	95.29±77.15	89.12±56.30	108.78±105.60	80.18±25.96	0.132	0.050
eGFR, mL/min/1.73 m^2	82.62±29.81	84.04±28.11	79.24±33.92	86.83±21.66	0.219*	0.130
Fasting glucose, mmol/L	9.55±3.12	9.31±2.64	10.08±3.74	8.95±2.56	0.281*	0.126
Duration between first-line medication and third-line medication (years), mean±SD	5.58±2.80	5.88±2.70	4.95±2.72	6.26±3.00	0.480*	0.107
Duration of DM (years), mean±SD	5.39±2.97	5.67±2.87	4.72±2.90	6.33±3.10	0.504*	0.094
Duration of DM, n (%)					0.305*	0.046
≤5 years	8773 (47.10%)	3717 (42.80%)	4086 (55.90%)	970 (36.83%)		
5–10 years	8587 (46.10%)	4363 (50.24%)	2941 (40.24%)	1283 (48.71%)		
>10 years	1268 (6.81%)	605 (6.97%)	282 (3.86%)	381 (14.46%)		
Charlson Comorbidity Index, n (%)					0.580*	0.045
1 or 2	2673 (12.99%)	1156 (11.61%)	1115 (14.37%)	402 (14.06%)		
3	4645 (22.57%)	2228 (22.38%)	1556 (20.05%)	861 (30.10%)		
4	4883 (23.73%)	2524 (25.35%)	1509 (19.45%)	850 (29.72%)		
5	3499 (17.00%)	1966 (19.74%)	1082 (13.94%)	451 (15.77%)		
6 or above	4877 (23.70%)	2083 (20.92%)	2498 (32.19%)	296 (10.35%)		

*Imbalance covariate if pairwise ASMD ≥0.2.
ASMD, absolute standardized mean difference; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TZD, thiazolidinediones.

The E-values as a sensitivity analysis for assessing unmeasured confounding bias were calculated for the HRs for cancer, cancer mortality, and all-cause mortality outcomes (online supplementary table 3). Since the E-values of those significant HRs were greater than all HRs of the measured confounders, it was unlikely that an unmeasured or unknown confounder would have greater effect on the outcomes than these known risk factors by having a HR exceeding those E-values (online supplementary table 4). Moreover, results in complete case analysis was also in line with those in the main analysis (online supplementary table 5).

The incidences of cancers, cancer mortality, and all-cause mortality were compared between patients with third-line medications and those without. A total of 176,879 patients with Met-SU therapy but without third-line medications were included. After removing patients who were under 18 years old (n=83), did not have T2DM

Table 2 Number and incidence rate of cancer, cancer mortality, and all-cause mortality

Event	Before weighting							After weighting	
	Cumulative incidence		Crude incidence rate (cases/100 person-years)			Median follow-up period (months)	Mean follow-up period (months)	Incidence rate (cases/100 person-years)	
	Cases with event	Rate	Estimate	95% CI*	Person-years			Estimate	95% CI*
Total (n=20 577)									
Cancer	571	0.028	0.97	(0.89 to 1.06)	58 687.17	28	34	1.00	(0.95 to 1.05)
Lip, oral cavity and pharynx	18	0.001	0.03	(0.02 to 0.05)	59 507.33	28	35	0.03	(0.03 to 0.04)
Digestive organs	248	0.012	0.42	(0.37 to 0.47)	59 240.67	28	35	0.41	(0.38 to 0.44)
Esophagus, stomach, and small intestine	22	0.001	0.04	(0.02 to 0.06)	59 514.25	28	35	0.03	(0.02 to 0.03)
Colorectum	105	0.005	0.18	(0.14 to 0.21)	59 382.92	28	35	0.19	(0.17 to 0.22)
Colon	75	0.004	0.13	(0.10 to 0.16)	59 441.92	28	35	0.15	(0.13 to 0.17)
Rectum/anus	43	0.002	0.07	(0.05 to 0.10)	59 460.92	28	35	0.09	(0.07 to 0.10)
Liver	56	0.003	0.09	(0.07 to 0.12)	59 459.83	28	35	0.08	(0.07 to 0.10)
Gallbladder and extrahepatic bile duct	22	0.001	0.04	(0.02 to 0.06)	59 516.08	28	35	0.05	(0.04 to 0.06)
Pancreas	46	0.002	0.08	(0.06 to 0.10)	59 513.58	28	35	0.06	(0.05 to 0.07)
Respiratory system	65	0.003	0.11	(0.08 to 0.14)	59 471.83	28	35	0.15	(0.13 to 0.17)
Bone, skin and soft tissure	22	0.001	0.04	(0.02 to 0.06)	59 498.33	28	35	0.04	(0.03 to 0.05)
Breast and genital organs (for female only)	84	0.009	0.32	(0.25 to 0.40)	26 283.00	28	35	0.27	(0.24 to 0.31)
Urinary organs	36	0.002	0.06	(0.04 to 0.08)	59 459.83	28	35	0.09	(0.08 to 0.11)
Eye, brain and central nervous system, endocrine glands	13	0.001	0.02	(0.01 to 0.04)	59 512.08	28	35	0.03	(0.02 to 0.03)
Lymphatic and hematopoietic tissue	43	0.002	0.07	(0.05 to 0.10)	59 492.92	28	35	0.05	(0.04 to 0.07)
Cancer mortality	179	0.009	0.31	(0.26 to 0.35)	58 538.83	28	34	0.29	(0.27 to 0.32)
All-cause mortality	1489	0.072	2.54	(2.42 to 2.68)	58 538.83	28	34	2.09	(2.02 to 2.16)
DPP4i as third-line medication (n=9957)									
Cancer	200	0.020	0.76	(0.66 to 0.87)	26 428.25	28	32	0.83	(0.75 to 0.91)
Lip, oral cavity, and pharynx	7	0.001	0.03	(0.01 to 0.05)	26 697.08	29	32	0.03	(0.01 to 0.04)
Digestive organs	76	0.008	0.29	(0.22 to 0.36)	26 629.33	28	32	0.32	(0.27 to 0.37)
Esophagus, stomach, and small intestine	7	0.001	0.03	(0.01 to 0.05)	26 710.33	29	32	0.03	(0.01 to 0.04)
Colorectum	37	0.004	0.14	(0.10 to 0.19)	26 662.08	28	32	0.15	(0.12 to 0.18)
Colon	28	0.003	0.10	(0.07 to 0.15)	26 677.50	28	32	0.11	(0.09 to 0.15)
Rectum/anus	14	0.001	0.05	(0.03 to 0.09)	26 693.17	29	32	0.06	(0.04 to 0.08)
Liver	17	0.002	0.06	(0.04 to 0.10)	26 694.17	29	32	0.07	(0.05 to 0.10)
Gallbladder and extrahepatic bile duct	4	0.000	0.01	(0.00 to 0.04)	26 710.58	29	32	0.01	(0.00 to 0.02)
Pancreas	11	0.001	0.04	(0.02 to 0.07)	26 706.33	29	32	0.06	(0.04 to 0.08)

Continued

Table 2 Continued

Event	Before weighting							After weighting	
	Cumulative incidence		Crude incidence rate (cases/100 person-years)			Median follow-up period (months)	Mean follow-up period (months)	Incidence rate (cases/100 person-years)	
	Cases with event	Rate	Estimate	95% CI*	Person-years			Estimate	95% CI*
Respiratory system	19	0.002	0.07	(0.04 to 0.11)	26 695.67	29	32	0.08	(0.06 to 0.11)
Bone, skin, and soft tissue	10	0.001	0.04	(0.02 to 0.07)	26 688.75	29	32	0.04	(0.03 to 0.06)
Breast and genital organs (for females only)	33	0.008	0.28	(0.20 to 0.40)	11 614.67	29	32	0.30	(0.24 to 0.38)
Urinary organs	15	0.002	0.06	(0.03 to 0.09)	26 691.42	29	32	0.05	(0.04 to 0.08)
Eye, brain and central nervous system, endocrine glands	5	0.001	0.02	(0.01 to 0.04)	26 703.25	29	32	0.02	(0.01 to 0.03)
Lymphatic and hematopoietic tissue	15	0.002	0.06	(0.03 to 0.09)	26 702.58	29	32	0.06	(0.04 to 0.08)
Cancer mortality	51	0.005	0.19	(0.14 to 0.25)	26 318.92	28	32	0.21	(0.17 to 0.25)
All-cause mortality	316	0.032	1.20	(1.07 to 1.34)	26 318.92	28	32	1.23	(1.14 to 1.33)
Insulin as third-line medication (n=7760)									
Cancer	336	0.043	1.21	(1.09 to 1.35)	27 700.75	39	43	0.97	(0.90 to 1.05)
Lip, oral cavity, and pharynx	9	0.001	0.03	(0.01 to 0.06)	28 193.67	40	44	0.03	(0.02 to 0.04)
Digestive organs	156	0.020	0.56	(0.47 to 0.65)	28 015.33	40	43	0.44	(0.39 to 0.49)
Esophagus, stomach, and small intestine	15	0.002	0.05	(0.03 to 0.09)	28 186.83	40	44	0.04	(0.03 to 0.06)
Colorectum	58	0.007	0.21	(0.16 to 0.27)	28 122.00	40	43	0.16	(0.13 to 0.20)
Colon	39	0.005	0.14	(0.10 to 0.19)	28 162.25	40	44	0.12	(0.09 to 0.15)
Rectum/anus	24	0.003	0.09	(0.05 to 0.13)	28 161.25	40	44	0.06	(0.04 to 0.08)
Liver	37	0.005	0.13	(0.09 to 0.18)	28 150.25	40	44	0.10	(0.07 to 0.12)
Gallbladder and extrahepatic bile duct	15	0.002	0.05	(0.03 to 0.09)	28 189.50	40	44	0.06	(0.04 to 0.08)
Pancreas	34	0.004	0.12	(0.08 to 0.17)	28 190.25	40	44	0.09	(0.07 to 0.11)
Respiratory system	40	0.005	0.14	(0.10 to 0.19)	28 170.83	40	44	0.12	(0.09 to 0.15)
Bone, skin, and soft tissue	10	0.001	0.04	(0.02 to 0.07)	28 194.42	40	44	0.04	(0.03 to 0.06)
Breast and genital organs (for females only)	48	0.014	0.38	(0.28 to 0.50)	12 734.17	42	44	0.30	(0.24 to 0.37)
Urinary organs	18	0.002	0.06	(0.04 to 0.10)	28 160.75	40	44	0.04	(0.03 to 0.06)
Eye, brain, and central nervous system, endocrine glands	7	0.001	0.02	(0.01 to 0.05)	28 192.67	40	44	0.02	(0.01 to 0.04)
Lymphatic and hematopoietic tissue	27	0.003	0.10	(0.06 to 0.14)	28 174.75	40	44	0.08	(0.06 to 0.10)
Cancer mortality	120	0.015	0.43	(0.36 to 0.52)	27 705.83	39	43	0.37	(0.32 to 0.42)
All-cause mortality	1135	0.146	4.10	(3.86 to 4.34)	27 705.83	39	43	3.22	(3.09 to 3.37)
TZD as third-line medication (n=2860)									
Cancer	35	0.012	0.77	(0.53 to 1.07)	4558.17	14	19	1.27	(1.16 to 1.38)

Continued

Table 2 Continued

Event	Before weighting							After weighting	
	Cumulative incidence		Crude incidence rate (cases/100 person-years)			Median follow-up period (months)	Mean follow-up period (months)	Incidence rate (cases/100 person-years)	
	Cases with event	Rate	Estimate	95% CI*	Person-years			Estimate	95% CI*
Lip, oral cavity, and pharynx	2	0.001	0.04	(0.01 to 0.16)	4616.58	14	19	0.05	(0.03 to 0.08)
Digestive organs	16	0.006	0.35	(0.20 to 0.57)	4596.00	14	19	0.47	(0.41 to 0.54)
Esophagus, stomach, and small intestine	0	0.000	0.00	NA†	4617.08	14	19	0.00	NA†
Colorectum	10	0.003	0.22	(0.10 to 0.40)	4598.83	14	19	0.30	(0.25 to 0.35)
Colon	8	0.003	0.17	(0.08 to 0.34)	4602.17	14	19	0.24	(0.20 to 0.30)
Rectum/anus	5	0.002	0.11	(0.04 to 0.25)	4606.50	14	19	0.17	(0.13 to 0.21)
Liver	2	0.001	0.04	(0.01 to 0.16)	4615.42	14	19	0.06	(0.04 to 0.09)
Gallbladder and extrahepatic bile duct	3	0.001	0.06	(0.01 to 0.19)	4616.00	14	19	0.09	(0.06 to 0.12)
Pancreas	1	0.000	0.02	(0.00 to 0.12)	4617.00	14	19	0.02	(0.01 to 0.04)
Respiratory system	6	0.002	0.13	(0.05 to 0.28)	4605.33	14	19	0.29	(0.24 to 0.34)
Bone, skin, and soft tissue	2	0.001	0.04	(0.01 to 0.16)	4615.17	14	19	0.04	(0.02 to 0.06)
Breast and genital organs (for females only)	3	0.002	0.16	(0.03 to 0.45)	1934.17	14	18	0.19	(0.13 to 0.26)
Urinary organs	3	0.001	0.07	(0.01 to 0.19)	4607.67	14	19	0.21	(0.17 to 0.26)
Eye, brain, and central nervous system, endocrine glands	1	0.000	0.02	(0.00 to 0.12)	4616.17	14	19	0.04	(0.03 to 0.07)
Lymphatic and hematopoietic tissue	1	0.000	0.02	(0.00 to 0.12)	4615.58	14	19	0.01	(0.00 to 0.03)
Cancer mortality	8	0.003	0.18	(0.08 to 0.35)	4514.08	14	19	0.30	(0.24 to 0.35)
All-cause mortality	38	0.013	0.84	(0.60 to 1.16)	4514.08	14	19	1.45	(1.34 to 1.57)

*The 95% CI was constructed based on Poisson distribution.
†Not available since no case for esophagus, stomach, and small intestine cancer with TZD as third-line medication.
DPP4i, dipeptidyl peptidase 4 inhibitor; NA, not applicable due to no observations; TZD, thiazolidinediones.

Table 3 HR of cancer, cancer mortality, and all-cause mortality

Event	TZD (vs DPP4i)			Insulin (vs TZD)			Insulin (vs DPP4i)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Cancer	1.43	(1.25 to 1.63)	<0.001*	0.81	(0.72 to 0.91)	<0.001*	1.15	(1.02 to 1.30)	0.024*
Lip, oral cavity, and pharynx	1.66	(0.81 to 3.40)	0.165	0.56	(0.30 to 1.08)	0.083	0.94	(0.46 to 1.91)	0.870
Digestive organs	1.47	(1.19 to 1.81)	<0.001*	0.94	(0.78 to 1.13)	0.528	1.38	(1.14 to 1.68)	<0.001*
Esophagus, stomach, and small intestine	NA†			NA†			1.27	(0.66 to 2.44)	0.479
Colorectum	2.06	(1.55 to 2.74)	<0.001*	0.53	(0.41 to 0.69)	<0.001*	1.10	(0.82 to 1.47)	0.526
Colon	2.26	(1.64 to 3.12)	<0.001*	0.45	(0.33 to 0.61)	<0.001*	1.02	(0.72 to 1.43)	0.928
Rectum/anus	3.01	(1.94 to 4.65)	<0.001*	0.34	(0.23 to 0.51)	<0.001*	1.03	(0.64 to 1.67)	0.907
Liver	0.78	(0.47 to 1.28)	0.322	1.61	(1.02 to 2.53)	0.041*	1.25	(0.83 to 1.86)	0.287
Gallbladder and extrahepatic bile duct	8.14	(3.36 to 19.69)	<0.001*	0.74	(0.46 to 1.17)	0.194	5.98	(2.48 to 14.42)	<0.001*
Pancreas	0.43	(0.20 to 0.89)	0.022*	3.97	(2.00 to 7.88)	<0.001*	1.69	(1.08 to 2.64)	0.021*
Respiratory system	3.60	(2.52 to 5.16)	<0.001*	0.40	(0.30 to 0.54)	<0.001*	1.45	(1.00 to 2.11)	0.050*
Bone, skin, and soft tissue	0.79	(0.41 to 1.51)	0.478	1.18	(0.63 to 2.22)	0.621	0.93	(0.53 to 1.63)	0.803
Breast and genital organs (for females only)	0.65	(0.43 to 0.97)	0.034*	1.54	(1.04 to 2.29)	0.031*	0.99	(0.73 to 1.36)	0.975
Urinary organs	2.30	(1.46 to 3.62)	<0.001*	0.25	(0.16 to 0.39)	<0.001*	0.58	(0.34 to 0.99)	0.045*
Eye, brain, and central nervous system, endocrine glands	2.63	(1.18 to 5.88)	0.018*	0.58	(0.29 to 1.16)	0.123	1.51	(0.65 to 3.52)	0.340
Lymphatic and hematopoietic tissue	0.18	(0.07 to 0.48)	<0.001*	6.72	(2.64 to 17.12)	<0.001*	1.24	(0.79 to 1.95)	0.352
Cancer mortality	1.21	(0.92 to 1.58)	0.172	1.36	(1.09 to 1.71)	0.007*	1.65	(1.31 to 2.07)	<0.001*
All-cause mortality	0.99	(0.88 to 1.11)	0.873	2.46	(2.25 to 2.70)	<0.001*	2.44	(2.23 to 2.67)	<0.001*
Sensitivity analysis - Pioglitazone only in TZD drug class									
Cancer	1.31	(1.13 to 1.50)	<0.001*	0.88	(0.77 to 1.00)	0.050	1.15	(1.01 to 1.30)	0.030*
Lip, oral cavity and pharynx	2.87	(1.44 to 5.69)	0.003*	0.30	(0.16 to 0.55)	<0.001*	0.85	(0.42 to 1.75)	0.674
Digestive organs	1.83	(1.49 to 2.25)	<0.001*	0.74	(0.62 to 0.89)	0.002*	1.36	(1.12 to 1.65)	0.002*
Esophagus, Stomach, and small intestine	NA†			NA†			1.27	(0.66 to 2.44)	0.481
Colorectum	2.45	(1.84 to 3.27)	<0.001*	0.45	(0.34 to 0.58)	<0.001*	1.09	(0.82 to 1.46)	0.564
Colon	2.65	(1.91 to 3.67)	<0.001*	0.38	(0.28 to 0.52)	<0.001*	1.01	(0.72 to 1.42)	0.965
Rectum / Anus	4.42	(2.87 to 6.82)	<0.001*	0.22	(0.15 to 0.33)	<0.001*	0.99	(0.61 to 1.60)	0.974
Liver	1.12	(0.69 to 1.80)	0.660	1.08	(0.70 to 1.68)	0.736	1.21	(0.81 to 1.81)	0.361
Gallbladder and extrahepatic bile duct	9.99	(4.14 to 24.07)	<0.001*	0.59	(0.37 to 0.93)	0.022*	5.87	(2.43 to 14.17)	<0.001*
Pancreas	0.55	(0.27 to 1.13)	0.105	3.02	(1.55 to 5.89)	0.001*	1.67	(1.07 to 2.62)	0.024*
Respiratory system	1.49	(0.98 to 2.26)	0.061	0.80	(0.56 to 1.15)	0.238	1.20	(0.82 to 1.75)	0.362

Continued

Table 3 Continued

Event	TZD (vs DPP4i)			Insulin (vs TZD)			Insulin (vs DPP4i)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Bone, skin and soft tissue	0.97	(0.51 to 1.85)	0.931	0.99	(0.53 to 1.84)	0.966	0.95	(0.54 to 1.68)	0.881
Breast and genital organs (for female only)	0.36	(0.21 to 0.62)	<0.001*	2.88	(1.67 to 4.97)	<0.001*	1.04	(0.76 to 1.42)	0.823
Urinary organs	2.31	(1.40 to 3.80)	0.001*	0.32	(0.19 to 0.53)	<0.001*	0.73	(0.43 to 1.25)	0.259
Eye, brain and central nervous system, endocrine glands	3.36	(1.53 to 7.41)	0.003*	0.45	(0.23 to 0.89)	0.022*	1.51	(0.65 to 3.52)	0.346
Lymphatic and haematopoietic tissue	0.26	(0.10 to 0.67)	0.005*	4.66	(1.88 to 11.55)	<0.001*	1.23	(0.78 to 1.94)	0.378
Cancer mortality	1.51	(1.15 to 1.98)	0.003*	1.00	(0.80 to 1.26)	0.991	1.51	(1.20 to 1.91)	<0.001*
All-cause mortality	1.13	(1.00 to 1.27)	0.044*	2.18	(1.97 to 2.41)	<0.001*	2.46	(2.25 to 2.69)	<0.001*
Sensitivity analysis—basal insulin only in insulin class									
Cancer	1.38	(1.21 to 1.57)	<0.001*	0.85	(0.75 to 0.95)	0.006*	1.17	(1.03 to 1.32)	0.015*
Lip, oral cavity, and pharynx	1.54	(0.70 to 3.42)	0.288	0.86	(0.45 to 1.65)	0.660	1.33	(0.64 to 2.77)	0.462
Digestive organs	1.25	(1.01 to 1.54)	0.038*	0.95	(0.78 to 1.15)	0.601	1.18	(0.98 to 1.43)	0.080
Esophagus, stomach, and small intestine	NA†			NA†			0.69	(0.38 to 1.27)	0.236
Colorectum	2.09	(1.56 to 2.80)	<0.001*	0.61	(0.47 to 0.79)	<0.001*	1.27	(0.95 to 1.70)	0.108
Colon	1.98	(1.41 to 2.79)	<0.001*	0.61	(0.45 to 0.82)	0.001*	1.21	(0.86 to 1.69)	0.283
Rectum/anus	3.14	(2.02 to 4.90)	<0.001*	0.39	(0.26 to 0.56)	<0.001*	1.21	(0.76 to 1.95)	0.433
Liver	0.47	(0.28 to 0.80)	0.005*	1.86	(1.12 to 3.06)	0.015*	0.88	(0.59 to 1.29)	0.517
Gallbladder and extrahepatic bile duct	3.98	(1.97 to 8.01)	<0.001*	0.55	(0.33 to 0.93)	0.026*	2.20	(1.08 to 4.46)	0.029*
Pancreas	0.39	(0.17 to 0.88)	0.023*	4.11	(1.90 to 8.89)	<0.001*	1.61	(1.00 to 2.59)	0.051
Respiratory system	4.47	(3.12 to 6.40)	<0.001*	0.37	(0.28 to 0.48)	<0.001*	1.63	(1.12 to 2.38)	0.010*
Bone, skin, and soft tissue	0.88	(0.44 to 1.75)	0.721	1.22	(0.64 to 2.34)	0.555	1.07	(0.59 to 1.95)	0.835
Breast and genital organs (for females only)	0.47	(0.30 to 0.73)	<0.001*	2.41	(1.58 to 3.67)	<0.001*	1.14	(0.84 to 1.54)	0.424
Urinary organs	1.82	(1.12 to 2.95)	0.015*	0.46	(0.30 to 0.70)	<0.001*	0.84	(0.51 to 1.38)	0.497
Eye, brain, and central nervous system, endocrine glands	2.20	(0.88 to 5.51)	0.092	0.79	(0.36 to 1.71)	0.562	1.74	(0.70 to 4.29)	0.234
Lymphatic and hematopoietic tissue	0.43	(0.20 to 0.90)	0.025*	3.42	(1.72 to 6.80)	<0.001*	1.47	(0.92 to 2.34)	0.106
Cancer mortality	0.91	(0.69 to 1.20)	0.507	1.44	(1.12 to 1.84)	0.004*	1.30	(1.04 to 1.63)	0.022*
All-cause mortality	0.89	(0.80 to 0.99)	0.027*	1.78	(1.63 to 1.95)	<0.001*	1.58	(1.45 to 1.72)	<0.001*
Sensitivity analysis—accounting for competing risk of death									
Cancer	1.46	(1.28 to 1.65)	<0.001*	0.77	(0.68 to 0.86)	<0.001*	1.12	(0.99 to 1.26)	0.083
Lip, oral cavity, and pharynx	1.74	(0.85 to 3.57)	0.131	0.52	(0.27 to 1.02)	0.058	0.91	(0.45 to 1.81)	0.794

Continued

Table 3 Continued

Event	TZD (vs DPP4i)			Insulin (vs TZD)			Insulin (vs DPP4i)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Digestive organs	1.49	(1.22 to 1.83)	<0.001*	0.90	(0.75 to 1.08)	0.261	1.34	(1.11 to 1.62)	0.003*
Esophagus, stomach, and small intestine	NA†			NA†			1.26	(0.64 to 2.47)	0.508
Colorectum	2.09	(1.59 to 2.74)	<0.001*	0.51	(0.39 to 0.66)	<0.001*	1.06	(0.80 to 1.42)	0.687
Colon	2.29	(1.69 to 3.11)	<0.001*	0.43	(0.32 to 0.58)	<0.001*	0.98	(0.70 to 1.37)	0.919
Rectum/anus	3.05	(2.01 to 4.63)	<0.001*	0.33	(0.22 to 0.49)	<0.001*	1.00	(0.62 to 1.61)	0.990
Liver	0.80	(0.51 to 1.25)	0.333	1.51	(0.98 to 2.34)	0.060	1.21	(0.81 to 1.81)	0.361
Gallbladder and extrahepatic bile duct	8.19	(3.42 to 19.60)	<0.001*	0.71	(0.44 to 1.14)	0.151	5.78	(2.40 to 13.91)	<0.001*
Pancreas	0.43	(0.20 to 0.93)	0.031*	3.80	(1.82 to 7.91)	<0.001*	1.64	(1.05 to 2.54)	0.028*
Respiratory system	3.66	(2.54 to 5.29)	<0.001*	0.38	(0.28 to 0.52)	<0.001*	1.40	(0.96 to 2.03)	0.080
Bone, skin, and soft tissue	0.80	(0.42 to 1.52)	0.508	1.12	(0.60 to 2.10)	0.737	0.90	(0.52 to 1.56)	0.716
Breast and genital organs (for females only)	0.65	(0.44 to 0.96)	0.030*	1.49	(1.01 to 2.21)	0.046*	0.96	(0.70 to 1.32)	0.829
Urinary organs	2.46	(1.63 to 3.72)	<0.001*	0.23	(0.15 to 0.35)	<0.001*	0.57	(0.33 to 0.96)	0.035*
Eye, brain, and central nervous system, endocrine glands	2.63	(1.25 to 5.51)	0.011*	0.56	(0.28 to 1.11)	0.099	1.47	(0.63 to 3.46)	0.381
Lymphatic and hematopoietic tissue	0.19	(0.08 to 0.46)	<0.001*	6.36	(2.58 to 15.64)	<0.001*	1.21	(0.75 to 1.93)	0.445

*Significantly different.
†Not available since no case for esophagus, stomach, and small intestine cancer with TZD as third-line medication.
DPP4i, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones.

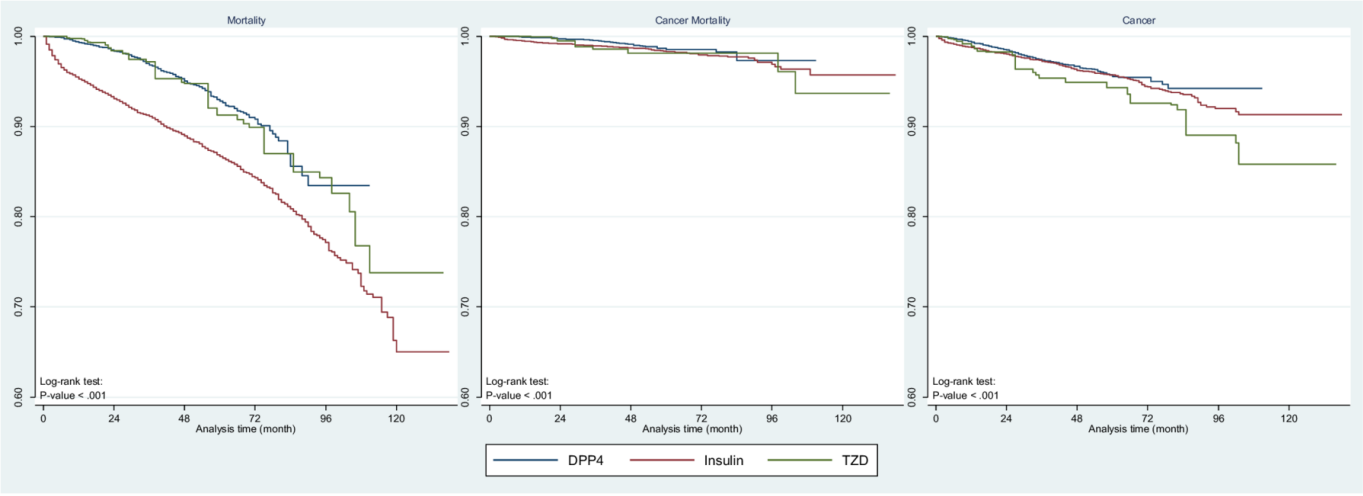

Figure 2 Kaplan-Meier survival curves for overall cancer, cancer-related mortality, and all-cause mortality for patients with type 2 diabetes mellitus with DPP4i, insulin, or TZD as third-line medications after propensity-score weighting. DPP4i, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones.

diagnosis codes (n=506), had previous cancer diagnoses (n=2834), or had first drug dispensing date before 2007 (n=36,349), a total of 137,107 were available for analysis. The baseline characteristics of 137,107 patients with T2DM with Met-SU therapy but without third-line medications are listed in online supplementary table 6. Compared with patients intensifying with third-line medications, patients without third-line medications had significantly lower risks of cancers (HR 1.16, 95% CI 1.06 to 1.26, p<0.001), cancer mortality (HR 1.44, 95% CI 1.23 to 1.68, p<0.001), and all-cause mortality (HR 3.73, 95% CI 3.52 to 3.95, p<0.001). Similar results were observed after patients were stratified by their baseline HbA1c level (<7% and ≥7%) (online supplementary tables 7 and 8).

DISCUSSION

Over the last few years, third-line glucose-lowering medications, which have been provided by the rising new classes of oral anti-glycemic agents, appear as an add-on approach to Met-SU.[27] To our knowledge, this is the first original study comparing the risks of cancers among patients with T2DM on Met-SU dual therapy with inadequate control, and intensified with DPP4i, insulin, or TZD as third-line medication.

The current study reveals that the third-line medication insulin was associated with the highest incidence of cancer mortality and all-cause mortality. This finding is consistent with our previous hypothesis that, comparing with patients initiated with DPP4i, patients with T2DM could be at an increased risk of cancer, cancer mortality, and all-cause mortality in pancreas while with insulin as third-line medication. A plausible explanation for an elevated cancer events as well as cancer mortality rate is that insulin increases circulating levels of insulin, poses mitogenic effects, and promotes pancreatic carcinogenesis.[28 29] Patients with T2DM have suffered from persistent insulin resistance. Meanwhile, the exogenous insulin therapy required in these patients causes substantially higher level of systemic hyper-insulinemic state. Nevertheless, insulin remains an effective, potent glucose-lowering agent with an overall established safety record. Therefore, it is considered as part of a combination therapy when hyperglycemia is severe and poorly controlled with the use of oral agents alone.[30] Basal insulin was shown to be associated with further reduction in all-cause mortality compared with other insulin regimens with overall higher dose. Such findings echoed with a Canadian guideline that a single daily dose of insulin NPH under the basal insulin regimen has been recommended to be initiated since 2013.[31] Though previous evidence supported the theory of "hyper-insulinemic colorectal cancer" among patients prescribed with insulin, our study did not show consistent findings, whereby TZD users had the greater risk of colon cancer than insulin users.[8 32]

Moreover, DPP4i was found to be associated with the lowest risk of cancer, cancer mortality, and all-cause mortality. As recommended by the latest clinical practice guideline, *Optimal Use Recommendations for Second- and Third-Line Therapy for Patients with Type 2 Diabetes*, DPP4i should be prescribed for patients who cannot tolerate insulin as the third-line medication.[31] There has been conflicting evidence on the association between DPP4i and the risk of cancer in the past. Despite previous increased rates of pancreatitis and pancreatic cancer reported, no final decision by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) could be made.[2 5 33] The association between DPP4i and cholangiocarcinoma has also been discussed in the past.[6] On the other hand, previous meta-analyses have concluded that DPP4i was not associated with all site-specific cancers compared with placebos and other glucose-lowering drugs.[5 34]

As another class of glucose-lowering agent, TZD regulates the circulating levels of insulin and decreases the

insulin resistance. Following the recommendation made by EMA in 2010 in suspending rosiglitazone due to an elevated cardiovascular ischemic risk, some studies have subsequently focused on assessing pioglitazone, a subclass of TZD. The risk of bladder cancer was found to be the highest in the present study. A safety announcement was issued by FDA in 2011 due to positive results showing the association between exposure of TZD for greater than 2 years and risk of bladder cancer.[10 11] Consistent results were also demonstrated in a nested case–control study conducted in the UK, with the risks of being the highest in patients exposed for more than 24 months and in those with cumulative dosages greater than 28,000 mg.[35] However, it is noteworthy that the absolute risks were low while the relative risks remained high. This is also reflected by a very low prevalence (<0.3%) of bladder cancer in patients with diabetes exposed to pioglitazone shown in a recent meta-analysis.[10] Nevertheless, its association could not excluded in meta-analysis with a statistically insignificant raised risk.[12] A similar study examined the effects of pioglitazone on survival rates in patients with active urothelial cancer of the bladder undergoing radical cystectomy. It turned out to be similar survival rates of patients with and without pioglitazone as the result, with an increased risk observed early on that had resolved with long-term follow-up.[11]

Strengths and limitations

Strengths of our study include the use of population-based cohort with a large sample for analysis, and the use of active comparator, implementation of a screening period, adjustment for important observed characteristics such as duration of diabetes, time exposed to glucose-lowering medications, and laboratory data in propensity-score weighting.[36] Several limitations are worthy of mention. First, as a retrospective cohort study, potential unmeasured confounding factors such as lifestyle risk factors, patient's motivation, cost considerations, and issues with drug adherence were not captured and may introduce selection bias. Other issues such that physicians tend to prescribe insulin to frail patients were also not included in the propensity-score weighting. These uncaptured factors could potentially exert an influence on the risks of cancer mortality and cancer events from developing, thereby reducing the validity of results. However, clinical equipoise across the groups was enhanced using propensity-score weighting, and likelihood that unmeasured confounders could affect the treatment–outcome relationship seemed unlikely, as indicated by E-values in sensitivity analysis. Second, issues with immortal person-time bias have not been dealt in current analysis literature and the methodological limitation could potentially hinder the evidence of the investigation by over-exaggerating the benefits observed within glucose-lowering drugs.[37] Furthermore, a limited duration of patients being prescribed with TZD could likely have weakened the strength of evidence of the study. Notably, the median length of follow-up varied across different third-line medications. Therefore, the risk of events might be underestimated from the data across a limited period of time. Since the overall duration of this study was relatively short, additional studies are needed in developing a full picture of the associated low risk of cancer of DPP4i as part of the third-line glucose-lowering medication for patients with T2DM treated with Met-SU dual therapy. Lastly, whether the risks were induced by the drug itself or by its effect on metabolism was uncertain; therefore, the causal relationship between taking third-line medication and risks of cancer or cancer mortality should be interpreted with caution.

CONCLUSIONS

Among the targeted patients with T2DM under inadequate control of Met-SU dual therapy, the addition of DPP4i was associated with lower risks of cancer and cancer mortality, and showed no increased risk for all-cause mortality. The third-line medication TZD was revealed to have the highest incidence and risk of cancer events, but comparing with insulin, it had insignificant differences in risks of cancer mortality and all-cause mortality. Moreover, in the subgroup of TZD, the association of pioglitazone with relatively lower risk of cancer events had been examined.

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Contributors CKHW had the original idea for the study, contributed to the development of the study, reviewed the literature, constructed the study design, conducted the statistical analysis, wrote the first draft of the manuscript, and acts as guarantor for the study. CKHW, KKCM, and TW provided critical input to the statistical analyses and design. EWYC, ICKW, and CLKL provided critical input to the study design. ETYT provided critical input to the diagnosis and drug dispensing codes from the database. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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