Diabetes and Metabolism 50 (2024) 101585

Contents lists available at ScienceDirect

Diabetes & Metabolism

journal homepage: www.elsevier.com/locate/diabet

Original article

# Association of SGLT2 inhibitors with incident cancer

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ARTICLE INFO

*Keywords:*
Cancer
Diabetes
Epidemiology
SGLT2i

ABSTRACT

*Aim:* It remains unknown whether sodium-glucose cotransporter 2 inhibitors (SGLT2i) could be associated with incident cancer.

*Methods:* We analyzed individuals having diabetes and newly prescribed SGLT2i or dipeptidyl peptidase 4 inhibitors (DPP4i) in a large-scale epidemiological database. The primary outcome was the incidence of cancer. A propensity score matching algorithm was employed to compare the subsequent development of cancer between the SGLT2i and DPP4i groups.

*Results:* After 1:2 propensity score matching, 26,823 individuals (8,941 SGLT2i, 17,882 DPP4i) were analyzed. During the mean follow-up duration of 2.0 ± 1.6 years, 1,076 individuals developed cancer. SGLT2i administration was associated with a reduced risk of cancer (HR 0.80, 95 % CI 0.70–0.91). Particularly, SGLT2i administration was related to a lower risk of colorectal cancer (HR 0.71, 95 % CI 0.50–0.998). Our primary findings remained consistent across various sensitivity analyses, including overlap weighting analysis (HR 0.79, 95 % CI 0.66–0.94), inverse probability of treatment weighting 0.75 (95 % CI 0.65–0.86), and induction period settings 0.78 (95 % CI 0.65–0.93). The risk of developing cancer was comparable among individual SGLT2is (*P*-value of 0.1738).

*Conclusion:* Our investigation using nationwide real-world data demonstrated the potential advantage of SGLT2i over DPP4i in reducing the development of cancer in individuals with diabetes.

## Introduction

Sodium-glucose cotransporter 2 inhibitor (SGLT2i), initially developed as a novel medication for diabetes, operates by hindering glucose reabsorption in the renal proximal tubule. This action facilitates the excretion of glucose through urine, thereby improving glycemic control. Recent clinical trials have extended the significance of SGLT2i beyond diabetes treatment, demonstrating its beneficial effects on heart failure and chronic kidney disease [1-3]. This has spurred increased clinical and scientific interest in these medications for individuals with diabetes. Additionally, diabetes is associated with an elevated risk of subsequent cancer development [4,5]. Prior experimental studies have suggested that SGLT2i might exhibit anticancer properties in various types of cancers [6-10]. While certain clinical studies, including randomized trials and observational studies, have explored the relationship between SGLT2i use and cancer development risk [11-16], the findings have been

*Abbreviations:* BMI, body mass index; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; SGLT2i, sodium-glucose cotransporter-2 inhibitor; WHO-ATC, World Health Organization Anatomical Therapeutic Chemical.

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https://doi.org/10.1016/j.diabet.2024.101585
Received 26 July 2024; Received in revised form 24 September 2024; Accepted 18 October 2024
Available online 24 October 2024

inconclusive, leaving this clinical question unresolved. In particular, results from the observational study of drug beneficial effect on cancer can be subject to several methodological limitations, such as time-related bias (immortal time bias and time-window bias) and selection bias (confounding by indication and prevalent user bias) [17-19]. Given the current surge in the usage of SGLT2i, a comprehensive examination of their potential association with cancer risk is imperative. Moreover, the verification of such an investigation necessitates the employment of large epidemiological cohorts, especially considering the generally low incidence of cancer development. In this context, our study leverages a nationwide epidemiological database to assess whether the use of SGLT2i is linked to a risk of cancer development with these limitations from previous literature in mind.

## Materials and methods

### *Study population*

Our study was a nationwide retrospective cohort analysis utilizing the DeSC database from DeSC Healthcare Inc., Tokyo, Japan [20-22]. This database is a comprehensive repository combining large-scale health checkups and administrative claims data spanning from April 2014 to November 2022. It integrates Japanese administrative records from three types of health insurers: salaried employees' association/union-administered health insurance from large companies, National Health Insurance for individuals under 75 years not employed, and the Advanced Elderly Medical Service System for those aged 75 years and over. Recognized for its wide-ranging inclusivity and dependability among the Japanese demographic, the DeSC database covers diverse age categories, from the young and middle-aged to older adults. To reduce bias from indication and unmeasured confounding factors, our methodology employed a new-user, active comparator approach (**Figure S1;** see supplementary materials associated with this article on line) [23]. Our control group consisted of individuals newly prescribed dipeptidyl peptidase 4 inhibitors (DPP4i) for diabetes. SGLT2i and DPP4i are common first-line medications for the treatment of diabetes in Japan [24]. Therefore, the basic characteristics of SGLT2i and DPP4i new users in Japan were considered to be relatively similar. From the database, we extracted 43,913 people with diabetes (defined by ICD-10 codes E10–E14) who began treatment with either SGLT2i or DPP4i. To avoid including individuals who had previously used these medications, we defined new usage as initiating either drug class in those who had never used either drug class within the past year. From this cohort, we excluded individuals having a history of any cancer (ICD-10 codes C00-C97) ($n = 5797$). After these exclusions, the study comprised 38,116 participants (as shown in **Figure S2;** see supplementary materials associated with this article on line).

### *Ethics*

The Ethics Committee of the University of Tokyo granted approval for this study (approval number: 2021010NI). The requirement for informed consent was exempted due to the anonymization and de-identification of all data in the DeSC database.

### *Measurements and definitions*

We obtained the following data from the health checkups: body mass index (BMI), blood pressure, and laboratory data (hemoglobin A1c [HbA1c], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides). To better characterize the patients' health status and disease burden at the time of treatment initiation, we obtained data on the presence of diabetic nephropathy (ICD-10 codes E102, E112, E122, E132, and E142), diabetic retinopathy (ICD-10 codes E103, E113, E123, E133, and E143), and diabetic neuropathy (ICD-10 codes E104, E114, E124, E134, and E144) at the date of prescription of SGLT2i or DPP4i based on the ICD-10 codes. Data on concomitant medications at the prescription date of SGLT2i or DPP4i were extracted from the administrative claims records.

### *Propensity score matching*

A propensity score-matching algorithm was used to generate a matched cohort to compare the benefits of SGLT2i and DPP4i use. As DPP4i is the most frequently prescribed diabetes medication in Japan and is believed to have no impact on the risk of cancer development, DPP4i was set as the reference [24]. We estimated the propensity scores of the SGLT2i users using a logistic regression model. To estimate the propensity score, we included the following variables: age, sex, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, use of medications (insulin, glucagon-like peptide-1 receptor agonist, biguanide, sulfonylurea, α-glucosidase inhibitor, thiazolidine, glinide, renin angiotensin system inhibitors, β-blockers, calcium channel blockers, mineralocorticoid receptor antagonists, diuretics, and statins), and year of SGLT2i or DPP4i prescription. SGLT2i and DPP4i users were matched using a 1:2 matching protocol (caliper width equal to 0.2 standard deviations of the logit score).

### *Outcomes*

Outcomes were obtained from administrative records between April 2014 and November 2022. The primary outcome was incident total cancer (ICD-10 codes C00-C97). The secondary outcome was incident 16 selected cancers. We selected these 16 cancers according to their incidence in Japan[25]. Because of the small number of events, cervical and uterine cancer were combined into one endpoint. ICD-10 codes for each cancer are provided in the **Table S1;** see supplementary materials associated with this article on line. We followed the study participants from the index date (i.e., initiation of SGLT2i or DPP4i) to the incidence of cancer, discontinuation of insurance, death, or study end date (November 2022).

### *Statistical analysis*

Descriptive statistics were presented in terms of the median (with interquartile range) and number (as a percentage). To contrast the clinical profiles of individuals using SGLT2i with those on DPP4i, standardized mean differences were employed. We compared the cumulative incidence of cancer between SGLT2i and DPP4i groups using Kaplan-Meier curves. The risk of cancer development in people treated with SGLT2i versus those on DPP4i was quantified using hazard ratios (HRs) along with 95 % confidence intervals (95 % CIs), calculated through a Cox proportional hazards regression analysis. If a significant difference in the risk of total cancer was detected between SGLT2i and DPP4i users, we performed a Cox proportional hazards regression analysis to compare the subsequent risk of total cancer among individual SGLT2is (Dapagliflozin, Empagliflozin, Canagliflozin, Tofogliflozin, Ipragliflozin and Luseogliflozin) to examine whether the effects of SGLT2i would be considered a class effect. Considering the number of cases, dapagliflozin was used as the reference. The model was adjusted for the same variables used in the propensity score-matching. We performed the Wald test to compare the HRs among individual SGLT2is.

We performed six sensitivity analyses to assess the robustness of the association between the use of SGLT2i and the risk of developing cancer. First, we performed an analysis using overlap weighting to balance the exposure groups (SGLT2i and DPP4i). SGLT2i users were weighted by the probability of prescribing DPP4i (1 − propensity score), whereas DPP4i users were weighted by the probability of prescribing SGLT2i (propensity score). Second, we adapted inverse probability of treatment weighting (IPTW) to reduce the imbalance in potential confounding

variables between SGLT2i and DPP4i users. We constructed a propensity score using a logistic regression model. Weights were based on the propensity score. Stabilized IPTW was performed to mitigate the influence of small estimated probabilities from the propensity score model. Third, we limited study participants to 18,162 individuals with type 2 diabetes defined as ICD-10 code of E11, whereas we extracted people with diabetes (ICD-10 codes E10–E14) in the primary analysis. Fourth, additional adjustments were made for lifestyle factors (smoking [current or noncurrent/never], alcohol consumption [daily or not every day], and exercise habits [active or inactive]) that the participants reported using a questionnaire at the time of the health examination. Approximately 27.2 % of all participants had missing values for one or more of these items. Consequently, individuals with missing values ($n = 10,351$) were excluded from the analysis. Exercise habits (inactive) was defined as not exercising for 30 min $\geq$ twice a week or not walking for more than an hour per day. Fifth, we set a one-year induction period. Sixth, we conducted subgroup analyses stratified by age ($\geq$ 65 and $<$ 65 years), sex, and BMI value ($\geq$ 25.0 and $<$ 25.0 kg/m$^2$). All statistical analyses were performed using STATA version 18 (StataCorp LLC, College Station, TX, USA).

## Results

### *Clinical characteristics*

Table I presents the baseline clinical characteristics of the study participants before and after propensity score matching. After 1:2 propensity score matching, 26,823 individuals (8941 SGLT2i, 17,882 DPP4i) were analyzed. The individual distributions were well balanced between SGLT2i and DPP4i users. The median age was 66 (54–71) years for SGLT2i users and 65 (53–71) years for DPP4i users. In addition, 5758 (64.4 %) individuals were men in SGLT2i users, and 11,684 (65.3 %) individuals were men in DPP4i users. The median BMI and HbA1c were 26.7 (24.1–29.9) and 6.8 % (6.3–7.4) in SGLT2i users, and 26.8 (24.0–30.4) and 6.9 % (6.4–7.4) in DPP4i users, respectively.

### *Risk of developing cancer between SGLT2i and DPP4i*

Cancer event was seen in 1076 individuals during the mean follow-up duration was 2.0 $\pm$ 1.6 years. After propensity score matching, Kaplan-Meier curves showed that the cumulative incidence of total cancer was lower in SGLT2i users than in DPP4i users (Log-rank $P <$ 0.001) (Fig. 1). Further, the Cox regression analysis presented that the

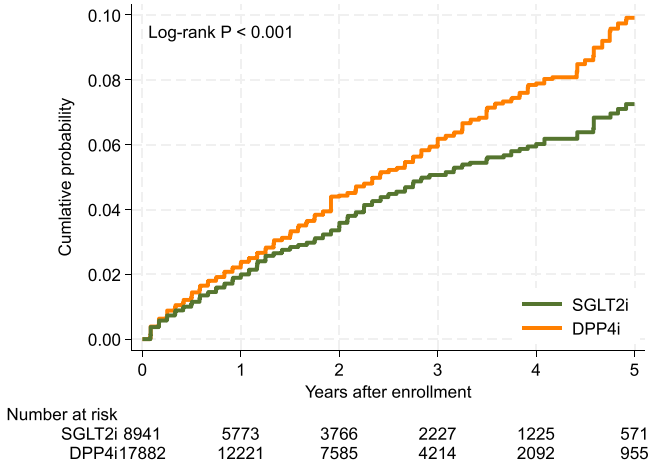


**Fig. 1.** Kaplan-Meier Curves.
Kaplan-Meier curves for total cancer.

**Table I**
Baseline Characteristics.

| | Before propensity score matching | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | DPP4i ($n = 29,175$) | SGLT2i ($n = 8941$) | SMD | DPP4i ($n = 17,882$) | SGLT2i ($n = 8941$) | SMD |
| Age, years | 68 (62–72) | 66 (54–71) | −0.326 | 65 (53–71) | 66 (54–71) | 0.042 |
| Men, n (%) | 17,245 (59.1) | 5758 (64.4) | 0.109 | 11,684 (65.3) | 5758 (64.4) | −0.02 |
| BMI, kg/m$^2$ | 24.7 (22.4–27.3) | 26.7 (24.1–29.9) | 0.497 | 26.8 (24.0–30.4) | 26.7 (24.1–29.9) | −0.057 |
| SBP, mmHg | 133 (123–144) | 132 (123–144) | −0.025 | 132 (122–144) | 132 (123–144) | 0.001 |
| DBP, mmHg | 77 (70–85) | 79 (71–86) | 0.116 | 79 (71–86) | 79 (71–86) | −0.02 |
| ***Comorbidity*** | | | | | | |
| Diabetic nephropathy, n (%) | 2641 (9.1) | 1082 (12.1) | 0.099 | 2032 (11.4) | 1082 (12.1) | 0.023 |
| Diabetic retinopathy, n (%) | 4470 (15.3) | 1468 (16.4) | 0.03 | 3041 (17.0) | 1468 (16.4) | −0.016 |
| Diabetic neuropathy, n (%) | 729 (2.5) | 280 (3.1) | 0.038 | 497 (2.8) | 280 (3.1) | 0.021 |
| ***Medication*** | | | | | | |
| Insulins, n (%) | 2262 (7.8) | 841 (9.4) | 0.059 | 1586 (8.9) | 841 (9.4) | 0.019 |
| GLP-1 Receptor Agonist, n (%) | 141 (0.5) | 337 (3.8) | 0.229 | 549 (3.1) | 337 (3.8) | 0.038 |
| Biguanide, n (%) | 6375 (21.9) | 2159 (24.1) | 0.055 | 4452 (24.9) | 2159 (24.1) | −0.017 |
| Sulfonylurea, n (%) | 2920 (10.0) | 634 (7.1) | −0.104 | 1253 (7.0) | 634 (7.1) | 0.003 |
| α-GI, n (%) | 2598 (8.9) | 623 (7.0) | −0.072 | 1229 (6.9) | 623 (7.0) | 0.004 |
| Thiazolidine, n (%) | 1275 (4.4) | 443 (5.0) | 0.028 | 913 (5.1) | 443 (5.0) | −0.007 |
| Glinides, n (%) | 924 (3.2) | 214 (2.4) | −0.047 | 395 (2.2) | 214 (2.4) | 0.012 |
| Renin angiotensin system inhibitor, n (%) | 11,554 (39.6) | 4500 (50.3) | 0.217 | 8935 (50.0) | 4500 (50.3) | 0.007 |
| Beta-blocker, n (%) | 2804 (9.6) | 1720 (19.2) | 0.277 | 3103 (17.4) | 1720 (19.2) | 0.049 |
| Calcium channel blocker, n (%) | 10,932 (37.5) | 3261 (36.5) | −0.021 | 6437 (36.0) | 3261 (36.5) | 0.01 |
| Mineralocorticoid receptor antagonist, n (%) | 657 (2.3) | 686 (7.7) | 0.252 | 1252 (7.0) | 686 (7.7) | 0.026 |
| Diuretics, n (%) | 2824 (9.7) | 1712 (19.1) | 0.272 | 3305 (18.5) | 1712 (19.1) | 0.017 |
| Statin, n (%) | 12,229 (41.9) | 4260 (47.6) | 0.115 | 8595 (48.1) | 4260 (47.6) | −0.008 |
| ***Laboratory Data*** | | | | | | |
| HbA1c, % | 6.9 (6.5–7.5) | 6.8 (6.3–7.4) | −0.133 | 6.9 (6.4–7.4) | 6.8 (6.3–7.4) | −0.034 |
| HbA1c, mmol/mol | 52 (48–58) | 51 (45–57) | −0.133 | 52 (46–57) | 51 (45–57) | −0.034 |
| LDL-C, mg/dl | 121 (101–144) | 119 (97–142) | −0.061 | 119 (98–141) | 119 (97–142) | −0.007 |
| HDL-C, mg/dl | 54 (45–65) | 52 (44–62) | −0.121 | 52 (44–62) | 52 (44–62) | 0.015 |
| Triglycerides, mg/dl | 127 (89–184) | 132 (93–194) | 0.055 | 134 (96–193) | 132 (93–194) | −0.002 |

Data are reported as medians (interquartile range) or numbers (percentage), where appropriate. DPP4i=dipeptidyl peptidase-4 inhibitors, SGLT2i=sodium-glucose cotransporter-2 inhibitors, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, GLP-1=glucagon-like peptide 1, α-GI=α-glucosidase inhibitor, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol.

risk of developing total cancer was reduced in individuals prescribed SGLT2i compared to those prescribed DPP4i (HR 0.80, 95 % CI 0.70–0.91). In almost all types of cancer, SGLT2i tended to reduce the risk of incident cancer when compared to DPP4i. Notably, in the group administered SGLT2i, there was a reduced risk of developing colorectal cancer compared to the group given DPP4i (HR 0.71, 95 % CI 0.50–0.998) (Fig. 2).

*Risk of developing cancer among individual SGLT2is*

We extracted SGLT2i users from the primary analysis after 1:2 propensity score matching. We excluded 19 individuals using multiple SGLT2is in this analysis. In the multivariable Cox regression analysis, compared to dapagliflozin, the risk of developing cancer did not differ among empagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin. The Wald tests showed that there was no statistically significant difference in the risk of total cancer among individual SGLT2is (p-value 0.1738) (Fig. 3).

*Sensitivity analyses*

First, the risk of developing cancer was lower in the SGLT2i users than in the DPP4i users after the overlap weighting procedure (HR 0.79, 95 % CI 0.66–0.94) (**Figure S3;** see supplementary materials associated with this article on line). Second, after IPTW, the HR of SGLT2i initiation for incident cancer was 0.75 (95 % CI 0.65–0.86) (**Figure S4;** see supplementary materials associated with this article on line). Third, we studied 18,162 individuals with a prior diagnosis of type 2 diabetes (ICD-10 code: E11). The HR (95 % CI) of SGLT2i for developing cancer was 0.70 (95 % CI 0.61–0.81) (**Figure S5;** see supplementary materials associated with this article on line). Fourth, even after including lifestyle habits (cigarette smoking, alcohol consumption, and physical inactivity) in estimating the propensity score, the administration of SGLT2i was related to a lower risk of developing cancer (HR 0.74, 95 % CI 0.64–0.87) (**Figure S6;** see supplementary materials associated with this article on line). Fifth, after setting an induction period of one year, we analyzed 17,331 individuals. The HR of SGLT2i for developing cancer was 0.78 (95 % CI 0.65–0.93) in this scenario (**Figure S7;** see supplementary materials associated with this article on line). The association between SGLT2i administration and individual cancers shown in the main analysis was also corroborated in most sensitivity analyses (**Figure S3-S7;** see supplementary materials associated with this article on line). Subgroup analyses stratified by age, sex, and BMI showed that SGLT2i initiation was associated with a decreased risk of developing total cancer in each subgroup (**Figure S8;** see supplementary materials associated with this article on line).

## Discussion

Our study utilized a nationwide, large-scale dataset derived from health check-ups and insurance claims, encompassing approximately 40,000 individuals diagnosed with diabetes newly prescribed SGLT2i or DPP4i. We compared the subsequent cancer development risk between users of SGLT2i and DPP4i following propensity score matching. The administration of SGLT2i was found to be associated with a lower risk of incident cancer in comparison to DPP4i administration. The findings from various sensitivity analyses aligned with this primary outcome. Additionally, the cancer development risk was similar across different SGLT2is. While several previous studies have examined the association between SGLT2i use and cancer risk, focusing on specific cancers such as bladder [26], breast [27], and colorectal cancer [28], a very recent cohort study from Hong Kong demonstrated a potential association between the administration of SGLT2i and a reduced overall cancer risk [14]. Our study contributes additional evidence by analyzing a large-scale epidemiological database in Japan to explore the overall cancer risk in Japanese patients treated with SGLT2i compared to those

| | DPP4i User | | SGLT2i User | | |
|---|---|---|---|---|---|
| **Primary Outcome** | Number | Event | Number | Event | HR (95% CI) |
| Total | 17,882 | 771 | 8,941 | 305 | 0.80 (0.70-0.91) |
| **Secondary Outcome** | | | | | |
| Colorectal | 17,882 | 126 | 8,941 | 44 | 0.71 (0.50-0.998) |
| Stomach | 17,882 | 91 | 8,941 | 32 | 0.71 (0.47-1.06) |
| Pancreas | 17,882 | 82 | 8,941 | 39 | 0.97 (0.66-1.42) |
| Lung | 17,882 | 82 | 8,941 | 34 | 0.84 (0.56-1.26) |
| Non-Hodgkin lymphoma | 17,882 | 50 | 8,941 | 20 | 0.81 (0.48-1.36) |
| Bladder | 17,882 | 38 | 8,941 | 16 | 0.84 (0.47-1.51) |
| Liver | 17,882 | 29 | 8,941 | 10 | 0.70 (0.34-1.43) |
| Esophagus | 17,882 | 25 | 8,941 | 7 | 0.57 (0.25-1.32) |
| Kidney | 17,882 | 19 | 8,941 | 11 | 1.16 (0.55-2.43) |
| Leukemia | 17,882 | 11 | 8,941 | 5 | 0.92 (0.32-2.64) |
| Thyroid | 17,882 | 7 | 8,941 | 3 | 0.87 (0.23-3.37) |
| Gallbladder | 17,882 | 7 | 8,941 | 2 | 0.59 (0.12-2.82) |
| Prostate (Men) | 11,516 | 106 | 5,758 | 46 | 0.86 (0.61-1.22) |
| Breast (Women) | 6,346 | 50 | 3,173 | 18 | 0.72 (0.42-1.24) |
| Cervical or Uterine (Women) | 6,346 | 27 | 3,173 | 10 | 0.72 (0.35-1.49) |

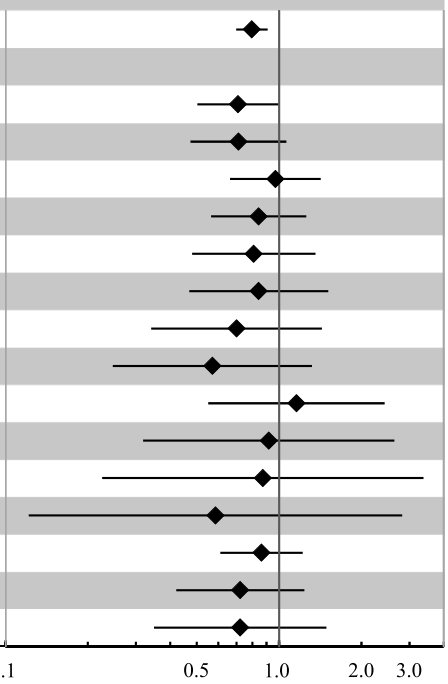


**Fig. 2.** Hazard Ratio of Developing Cancers.
We performed a Cox proportional hazards regression model to estimate the hazard ratio (HR) and 95 % confidence interval (95 % CI) of cancer with sodium-glucose cotransporter 2 inhibitors (SGLT2i) versus dipeptidyl peptidase-4 inhibitors (DPP4i) after 1:2 propensity score matching. Analysis for prostate cancer was performed only among men, whereas analysis for breast, cervical, and uterine cancer was performed only among women.

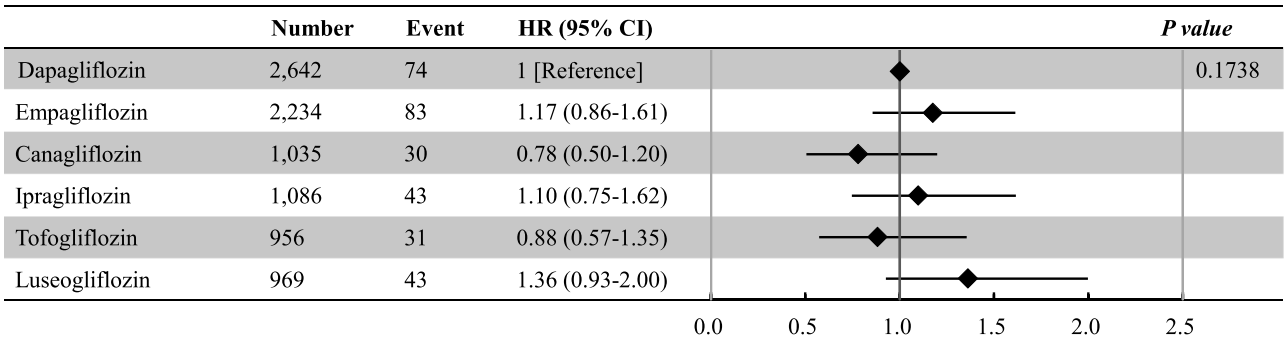


**Fig. 3.** Hazard Ratio of Developing Cancers among SGLT2is.
We performed a Cox proportional hazards regression model to estimate the hazard ratio (HR) and 95 % confidence interval (95 % CI) of cancer among individual sodium-glucose cotransporter 2 inhibitors (SGLT2is). We performed the Wald test to compare the HRs among individual SGLT2is.

treated with DPP4i.

Our research stands out from previous studies in several key aspects, and we believe it holds important implications for clinical practice.

First, to date, numerous large-scale clinical trials have been conducted on SGLT2i, establishing robust evidence for its role in preventing the worsening of heart failure and chronic kidney disease. However, among these trials utilizing SGLT2i, few have investigated cancer as an outcome, and, if any, their results have not been consistent. A recent meta-analysis, analyzing 77 randomized controlled trials which compared the therapeutic efficacy of SGLT2i with placebo or other hypoglycemic agents, reported no association between the use of SGLT2i and the risk of cancer development, yet the study was limited by insufficient adjustment for factors such as age, sex, and comorbidities [13]. Besides, other two meta-analyses also explored and confirmed the effects of SGLT2i on cancer [29,30]. In this regard, our research leveraged a vast epidemiological cohort, combining health check-up data and insurance claims records, and employed propensity score matching across a multitude of variables such as age, sex, comorbid diseases, and prescribed medications, to suggest a potential reduction in cancer risk among individuals with diabetes prescribed SGLT2i compared to those prescribed DPP4i. Particularly after propensity score matching, the Kaplan-Meier curves demonstrated a divergence in cancer risk one year after the initiation of either medication, with this disparity not only persisting over time but also widening, a finding of considerable significance. While studies with outcomes such as the exacerbation of heart failure have reported the immediate manifestation of benefits following the initiation of SGLT2i, considering the oncogenesis mechanism, the early emergence of anticancer effects from SGLT2i is unlikely. Instead, the observation of a decreased cancer risk in the longer term is reassuring. This was corroborated by sensitivity analyses even with a one-year induction period. Given the outcome of cancer development, ideally, an even longer induction period should be established, necessitating more extended observation, which remains an area for future investigation.

Second, it is important to note that in this study, the prescription of SGLT2i tends to have a protective effect compared to DPP4i for almost all individual cancer types. There had been concerns that the prescription of SGLT2i might increase the risk of cancer development in some cancer types (particularly bladder and kidney cancer) [13,15,31], but such trends were not observed in the analysis of this large-scale epidemiological cohort. Various pathophysiological mechanisms have been proposed regarding the potential of SGLT2i to reduce the risk of cancer development. The main ones include activation of AMP-activated protein kinase, inhibition of mitochondrial complex I, inhibition of glucose uptake, and activation of anticancer immune responses [32-34]. Needless to say, the mechanism of cancer development and the effect of SGLT2i vary greatly depending on the individual cancer type, requiring further experimental investigation. Particularly in this study, it was observed that the risk of developing colorectal cancer was lower in the SGLT2i group compared to the DPP4i group, in the main analysis as well as sensitivity analyses. Regarding colorectal cancer, experimental studies have reported that SGLT2i may inhibit cancer growth [16,35,36], and our findings are patho-physiologically reasonable. It is necessary to verify these results using prospective registration studies or cohorts with longer observation periods.

Third, if there were a possibility that SGLT2i had a protective effect against cancer development, to verify whether this effect is a class effect, we analyzed the risk of cancer development among individual SGLT2is. As shown in Fig. 3, no statistically significant differences in the risk of cancer development were observed among the six types of SGLT2i commercially available in Japan. Although a recent report has suggested that the influence on cancer development risk might differ among individual SGLT2is [13], such distinctions were not detected in our analysis. However, it is necessary to consider that dividing the study population by individual SGLT2i could have reduced the statistical power.

The strength of this study lies in its use of a large-scale, nationwide epidemiological cohort, enabling a variety of sensitivity analyses to confirm the robustness of our primary outcomes. The main results are consistent with those of a very recent cohort study from Hong Kong [14], and we believe that the adoption of very rigorous new-user design in this study has yielded convincing results. Our study has inherent limitations, mainly due to the use of our database, as previously described [37,38]. Due to the observational and retrospective nature of the present study, and despite robust statistical procedures, including propensity score matching and a multitude of sensitivity analyses, the possibility of unmeasured residual confounding effects could not be eliminated. It is unknown whether our findings can be applied to other population because the DeSC database primarily includes Japanese. Recorded diagnoses of administrative data are generally considered less well-validated; therefore, uncertainty remains regarding the accuracy of cancer diagnoses. However, the validity of the diagnoses of the administrative database in Japan has been reported to be high. For example, the sensitivity and specificity of cancer diagnoses were 83.5 % and 97.7 % [39]. Several critical information for specific cancers (e.g., hepatitis B or C virus for liver cancer, human papilloma virus for uterine cervix cancer, and Helicobacter pylori for stomach cancer) was absent. The types of cancer (e.g., adenocarcinoma or squamous cell carcinoma as described for esophageal cancer) could not be identified in the current study. In this study, the DPP4i user group was set as the reference group. Based on previous investigations that DPP4is do not affect the risk of cancer development [40], DPP4is were considered appropriate as an 'active comparator' for SGLT2is. However, it is necessary to recognize that this is not a comparison between a placebo and SGLT2i, as would be the case in a randomized controlled trial. Furthermore, we could not extract data on the cause of death; therefore, it was difficult to examine the association between the use of SGLT2i and cancer-related death. Finally, the dosages of SGLT2i and DPP4i were not considered in this

study, but they are likely relevant to their capacity for risk reduction, particularly given the dose-dependent nature of SGLT2i's anticancer effects, which have been reported in the previous basic research [41-43].

## Conclusions

Individuals with diabetes who were newly prescribed SGLT2i showed a reduced risk of developing cancer compared to those who were newly prescribed DPP4i. The findings of this study shed light on novel potential benefits of SGLT2i in our clinical practice.

## Source of funding

This work was supported by grants from Japan Foundation for Applied Enzymology (to T.K.), Sakakibara Heart Foundation Cardiovascular Research Program 2023 (to T.K.), Japanese Circulation Society (to T.K.), Takeda Science Foundation (to T.K.), Japan Heart Foundation (to T.K.), AMED JP23ek0109600h0003 (to T.K.), the Ministry of Health, Labour and Welfare, Japan (23AA2003 to H. Y.), and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907 and 21H03159 to H. Y, 21K08123 to H.K, and 22K21133 to Y.S.). The funding sources played no role in the current study.

## IRB information

Name of the ethics committee: the Clinical Research Review Board of The University of Tokyo [2021010NI].

## CRediT authorship contribution statement

**Yuta Suzuki:** Writing – original draft, Formal analysis, Conceptualization. **Hidehiro Kaneko:** Writing – review & editing, Writing – original draft, Resources, Project administration, Conceptualization. **Akira Okada:** Writing – original draft, Formal analysis, Conceptualization. **Toshiyuki Ko:** Writing – original draft, Formal analysis, Conceptualization. **Takahiro Jimba:** Writing – original draft, Formal analysis, Conceptualization. **Katsuhito Fujiu:** Writing – original draft, Formal analysis, Conceptualization. **Norifumi Takeda:** Writing – original draft, Formal analysis, Conceptualization. **Hiroyuki Morita:** Writing – review & editing, Conceptualization. **Jin Komuro:** Writing – original draft, Formal analysis. **Masaki Ieda:** Writing – review & editing, Supervision, Project administration. **Koichi Node:** Writing – review & editing, Supervision. **Issei Komuro:** Writing – review & editing, Supervision. **Hideo Yasunaga:** Writing – review & editing, Supervision, Project administration, Formal analysis, Data curation. **Norihiko Takeda:** Writing – review & editing, Supervision, Conceptualization.

## Declaration of competing interest

Research funding and scholarship funds (Hidehiro Kaneko and Katsuhito Fujiu) from Medtronic Japan CO., LTD, Boston Scientific Japan CO., LTD, Biotronik Japan, Simplex QUANTUM CO., LTD, and Fukuda Denshi, Central Tokyo CO., LTD. Hidehiro Kaneko owns stocks of PrevMed Co. Issei Komuro received remuneration for a lecture from AstraZeneca K.K, MSD K.K, Otsuka Pharmaceutical Co. Ltd., ONO PHARMACEUTICAL CO. LTD., DAIICHI SANKYO COMPANY LIMITED., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co. Ltd., BAYER YAKUHIN, LTD., Novo Nordisk Pharma Ltd., Pfizer Japan Inc and trust research/joint research funds from ONO PHARMACEUTICAL CO. LTD. and scholarship fund from Idorsia Pharmaceuticals Japan Ltd., MSD K.K., ONO PHARMACEUTICAL CO. LTD., Sanofi K. K., DAIICHI SANKYO COMPANY LIMITED., Dainippon Sumitomo Pharma Co. Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, TEIJIN PHARMA LIMITED, TOA EIYO LTD.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2024.101585.

## Appendix supplementary material

Supplementary materials (Figures S1-S8 and Table S1) associated with this article can be found at http://www.scincedirect.com at doi:10.1016/j.diabet.2024.101585.

## References

[1] Scheen AJ. Sodium-glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2020;16:556–77. https://doi.org/10.1038/s41574-020-0392-2.
[2] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020;17:761–72. https://doi.org/10.1038/s41569-020-0406-8.
[3] Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752–72. https://doi.org/10.1161/circulationaha.116.021887.
[4] Ling S, Brown K, Miksza JK, Howells L, Morrison A, Issa E, et al. Association of type 2 diabetes with cancer: a meta-analysis with bias analysis for unmeasured confounding in 151 cohorts comprising 32 million people. Diabetes Care 2020;43:2313–22. https://doi.org/10.2337/dc20-0204.
[5] Bjornsdottir HH, Rawshani A, Rawshani A, Franzen S, Svensson AM, Sattar N, et al. A national observation study of cancer incidence and mortality risks in type 2 diabetes compared to the background population over time. Sci Rep 2020;10:17376. https://doi.org/10.1038/s41598-020-73668-y.
[6] Villani LA, Smith BK, Marcinko K, Ford RJ, Broadfield LA, Green AE, et al. The diabetes medication Canagliflozin reduces cancer cell proliferation by inhibiting mitochondrial complex-I supported respiration. Mol Metab 2016;5:1048–56. https://doi.org/10.1016/j.molmet.2016.08.014.
[7] Li H, Tong CW, Leung Y, Wong MH, To KK, Leung KS. Identification of clinically approved drugs indacaterol and canagliflozin for repurposing to treat epidermal growth factor tyrosine kinase inhibitor-resistant lung cancer. Front Oncol 2017;7:288. https://doi.org/10.3389/fonc.2017.00288.
[8] Ding L, Chen X, Zhang W, Dai X, Guo H, Pan X, et al. Canagliflozin primes antitumor immunity by triggering PD-L1 degradation in endocytic recycling. J Clin Invest 2023;133:e154754. https://doi.org/10.1172/JCI154754.
[9] Scafoglio C, Hirayama BA, Kepe V, Liu J, Ghezzi C, Satyamurthy N, et al. Functional expression of sodium-glucose transporters in cancer. Proc Natl Acad Sci U S A 2015;112:E4111–9. https://doi.org/10.1073/pnas.1511698112.
[10] Scafoglio CR, Villegas B, Abdelhady G, Bailey ST, Liu J, Shirali AS, et al. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. Sci Transl Med 2018;10:eaat5933. https://doi.org/10.1126/scitranslmed.aat5933.
[11] Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diabetes Metab Syndr Obes 2012;5:313–27. https://doi.org/10.2147/DMSO.S22545.
[12] Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia 2017;60:1862–72. https://doi.org/10.1007/s00125-017-4370-8.
[13] Shi N, Shi Y, Xu J, Si Y, Yang T, Zhang M, et al. SGLT-2i and risk of malignancy in type 2 diabetes: a meta-analysis of randomized controlled trials. Front Public Health 2021;9:668368. https://doi.org/10.3389/fpubh.2021.668368.
[14] Chung CT, Lakhani I, Chou OHI, Lee TTL, Dee EC, Ng K, et al. Sodium-glucose cotransporter 2 inhibitors versus dipeptidyl peptidase 4 inhibitors on new-onset overall cancer in Type 2 diabetes mellitus: a population-based study. Cancer Med 2023;12:12299–315. https://doi.org/10.1002/cam4.5927.
[15] Xu B, Kang B, Li S, Fan S, Zhou J. Sodium-glucose cotransporter 2 inhibitors and cancer: a systematic review and meta-analysis. J Endocrinol Inves 2024;47:2421–36. https://doi.org/10.1007/s40618-024-02351-0.
[16] Chiang CH, Chiang CH, Hsia YP, Jaroenlapnopparat A, Horng CS, Wong KY, et al. The impact of sodium-glucose cotransporter-2 inhibitors on outcome of patients with diabetes mellitus and colorectal cancer. J Gastroenterol Hepatol 2024;39:902–7. https://doi.org/10.1111/jgh.16498.
[17] Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35:2665–73. https://doi.org/10.2337/dc12-0788.
[18] Acton EK, Willis AW, Hennessy S. Core concepts in pharmacoepidemiology: key biases arising in pharmacoepidemiologic studies. Pharmacoepidemiol Drug Saf 2023;32:9–18. https://doi.org/10.1002/pds.5547.
[19] Sendor R, Stürmer T. Core concepts in pharmacoepidemiology: confounding by indication and the role of active comparators. Pharmacoepidemiol Drug Saf 2022;31:261–9. https://doi.org/10.1002/pds.5407.
[20] Okada A, Yasunaga H. Prevalence of noncommunicable diseases in Japan using a newly developed administrative claims database covering young, middle-aged, and elderly people. JMA J 2022;5:190–8. https://doi.org/10.31662/jmaj.2021-0189.

[21] Ohbe H, Goto T, Okada A, Yasunaga H. Association between Covid-19 pandemic and mental disorders in spouses of intensive care unit patients. Intensive Care Med 2023;49:112–4. https://doi.org/10.1007/s00134-022-06941-5.
[22] Konish T, Ono S, Okada A, Matsui H, Tanabe M, Seto Y, et al. Comparison of bleeding following gastrointestinal endoscopic biopsy in patients treated with and without direct oral anticoagulants. Endosc Int Open 2023;11:E52–9. https://doi.org/10.1055/a-1981-2946.
[23] Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915–20. https://doi.org/10.1093/aje/kwg231.
[24] Bouchi R, Sugiyama T, Goto A, Imai K, Ihana-Sugiyama N, Ohsugi M, et al. Retrospective nationwide study on the trends in first-line antidiabetic medication for patients with type 2 diabetes in Japan. J Diabetes Investig 2022;13:280–91. https://doi.org/10.1111/jdi.13636.
[25] Kaneko H, Yano Y, Lee HH, Lee H, Okada A, Itoh H, et al. Medication-naïve blood pressure and incident cancers: analysis of 2 nationwide population-based databases. Am J Hypertens 2022;35:731–9. https://doi.org/10.1093/ajh/hpac054.
[26] Abrahami D, Tesfaye H, Yin H, Vine S, Hicks B, Yu OHY, et al. Sodium-glucose cotransporter 2 inhibitors and the short-term risk of bladder cancer: an international multisite cohort study. Diabetes Care 2022;45:2907–17. https://doi.org/10.2337/dc22-1174.
[27] Wang F, Hendryx M, Liu N, Bidulescu A, Mitra AK, Luo J. SGLT2 inhibitor use and risk of breast cancer among adult women with type 2 diabetes. Drug Saf 2024;47:125–33. https://doi.org/10.1007/s40264-023-01373-6.
[28] Chan RNC, Chan RNF, Chou OHI, Tse G, Lee S. Lower risks of incident colorectal cancer in SGLT2i users compared to DPP4i users: a propensity score-matched study with competing risk analysis. Eur J Intern Med 2023;110:125–7. https://doi.org/10.1016/j.ejim.2023.01.021.
[29] Benedetti R, Benincasa G, Glass K, Chianese U, Vietri MT, Congi R, et al. Effects of novel SGLT2 inhibitors on cancer incidence in hyperglycemic patients: a meta-analysis of randomized clinical trials. Pharmacol Res 2022;175:106039. https://doi.org/10.1016/j.phrs.2021.106039.
[30] Spiazzi BF, Naibo RA, Wayerbacher LF, Piccoli GF, Farenzena LP, Londero TM, et al. Sodium-glucose cotransporter-2 inhibitors and cancer outcomes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2023;198:110621. https://doi.org/10.1016/j.diabres.2023.110621.
[31] Garcia M, Arteche-Martinez U, Lertxundi U, Aguirre C. SGLT2 inhibitors and bladder cancer: analysis of cases reported in the European pharmacovigilance database. J Clin Pharmacol 2021;61:187–92. https://doi.org/10.1002/jcph.1722.
[32] Dabour MS, George MY, Daniel MR, Blaes AH, Zordoky BN. The cardioprotective and anticancer effects of SGLT2 inhibitors. JACC: CardioOncol 2024;6:159–82. https://doi.org/10.1016/j.jaccao.2024.01.007.
[33] Dutka M, Bobinski R, Francuz T, Garczorz W, Zimmer K, Ilczak T, et al. SGLT-2 inhibitors in cancer treatment-mechanisms of action and emerging new perspectives. Cancers (Basel) 2022;14:5811. https://doi.org/10.3390/cancers14235811.
[34] Lau KTK, Ng L, Wong JWH, Loong HHF, Chan WWL, Lee CH, et al. Repurposing sodium-glucose co-transporter 2 inhibitors (SGLT2i) for cancer treatment - A review. Rev Endocr Metab Disord 2021;22:1121–36. https://doi.org/10.1007/s11154-021-09675-9.
[35] Nasiri AR, Rodrigues MR, Li Z, Leitner BP, Perry RJ. SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia. Cancer Metab 2019;7:10. https://doi.org/10.1186/s40170-019-0203-1.
[36] Okada J, Yamada E, Saito T, Yokoo H, Osaki A, Shimoda Y, et al. Dapagliflozin inhibits cell adhesion to collagen i and iv and increases ectodomain proteolytic cleavage of DDR1 by increasing ADAM10 activity. Molecules 2020;25:495. https://doi.org/10.3390/molecules25030495.
[37] Suzuki Y, Kaneko H, Okada A, Matsuoka S, Fujiu K, Michihata N, et al. Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors. Kidney Int 2022;102:1147–53. https://doi.org/10.1016/j.kint.2022.05.031.
[38] Suzuki Y, Kaneko H, Okada A, Itoh H, Matsuoka S, Fujiu K, et al. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. Cardiovasc Diabetol 2022;21:67. https://doi.org/10.1186/s12933-022-01508-6.
[39] Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol 2017;27:476–82. https://doi.org/10.1016/j.je.2016.09.009.
[40] Zhao M, Chen J, Yuan Y, Zou Z, Lai X, Rahmani DM, et al. Dipeptidyl peptidase-4 inhibitors and cancer risk in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. Sci Rep 2017;7:8273. https://doi.org/10.1038/s41598-017-07921-2.
[41] Basak D, Gamez D, Deb S. SGLT2 inhibitors as potential anticancer agents. Biomedicines 2023;11:1867. https://doi.org/10.3390/biomedicines11071867.
[42] Sun M, Sun J, Sun W, Li X, Wang Z, Sun L, et al. Unveiling the anticancer effects of SGLT-2i: mechanisms and therapeutic potential. Front Pharmacol 2024;15:1369352. https://doi.org/10.3389/fphar.2024.1369352.
[43] Dabour MS, George MY, Daniel MR, Blaes AH, Zordoky BN. The cardioprotective and anticancer effects of sglt2 inhibitors: JACC: CardioOncology State-of-the-Art Review. JACC Cardio Oncol 2024;6:159–82. https://doi.org/10.1016/j.jaccao.2024.01.007.