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ORIGINAL RESEARCH

Impact of SGLT2 Inhibitors on Tumor Development Risk in Type 2 Diabetes: A Retrospective Cohort Study

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Aim: To assess the association between sodium-glucose cotransporter 2 (SGLT2) inhibitor use and the risk of tumor development and survival outcomes in patients with type 2 diabetes.

Methods: This retrospective cohort study included 350 patients with type 2 diabetes treated at our institution between January 2021 and January 2025. Patients were categorized into an observation group (n = 189) receiving SGLT2 inhibitors and a control group (n = 161) treated with other antidiabetic medications. Clinical characteristics, glycemic control, cumulative drug exposure, and tumor incidence (lung, colorectal, prostate, breast, bladder, and hepatic cancers) were analyzed. Kaplan–Meier methods were used to evaluate cancer incidence and mortality outcomes.

Results: Overall tumor incidence was significantly lower in the SGLT2 inhibitor group than in the control group ($P < 0.001$), mainly due to reduced lung ($P = 0.018$) and ovarian cancers ($P = 0.017$). Smoking, alcohol consumption, and poor glycemic control were associated with higher overall and site-specific tumor risks. The SGLT2 inhibitor group showed better metabolic profiles, with lower FBG, HbA1c, LDL, TC, TG, and higher HDL levels (all $P < 0.05$), as well as improved renal function indicated by lower BUN and creatinine and higher eGFR (all $P < 0.001$). Kaplan–Meier analysis demonstrated significantly longer progression-free and overall survival in the SGLT2 inhibitor group (both $P < 0.01$).

Conclusion: SGLT2 inhibitors reduced overall tumor risk, especially lung and ovarian cancers, and improved metabolic and survival outcomes in type 2 diabetes.

Keywords: diabetes medication, tumor development, SGLT2 inhibitors

Introduction

The global prevalence of type 2 diabetes (T2D) continues to rise, now affecting over 400 million individuals worldwide.[1] Beyond its well-established complications such as cardiovascular disease and kidney failure, T2D has also been recognized as an independent risk factor for various malignancies, including cancers of the liver, colon, pancreas,and breast[2] The mechanisms linking diabetes to cancer are multifactorial and involve hyperinsulinemia, chronic inflammation, oxidative stress, and metabolic reprogramming.[3] Therefore, antidiabetic therapies that improve metabolic control and mitigate these pathophysiological processes may also influence cancer development.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a novel class of glucose-lowering agents that improve glycemic control by reducing renal glucose reabsorption and increasing urinary glucose excretion.[4] In addition to their established cardioprotective and renoprotective benefits, recent studies suggest that SGLT2 inhibitors may exert anti-tumor effects through several biological pathways.[5,6] Mechanistically, these agents may attenuate tumor-promoting inflammation by downregulating pro-inflammatory cytokines such as TNF-α and IL-6, enhance insulin sensitivity to

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reduce insulin-mediated cell proliferation, and limit glucose availability within tumor microenvironments.[7] Furthermore, emerging evidence indicates that SGLT2 inhibition could modulate insulin-like growth factor (IGF) signaling, mitochondrial metabolism, and reactive oxygen species (ROS) generation—key processes implicated in tumorigenesis.[8]

Recent study reported improved survival outcomes among diabetic patients with non-small-cell lung cancer treated with SGLT2 inhibitors.[9,10] Similarly, updated meta-analyse have highlighted possible reductions in overall cancer incidence, though findings remain inconsistent across cancer types.[11] Despite these encouraging results, few large-scale clinical studies have directly examined the relationship between SGLT2 inhibitor use and cancer incidence, and the long-term oncological safety of these drugs remains uncertain.

To address this knowledge gap, the present retrospective cohort study investigates the association between SGLT2 inhibitor use and tumor development risk in patients with T2D. By integrating clinical outcomes, drug exposure metrics, and survival analyses, this study aims to clarify whether SGLT2 inhibitors confer protective effects against specific cancers while improving metabolic and renal health outcomes in this patient population.

Methods

Case Selection

This retrospective study included 350 patients diagnosed with type 2 diabetes who sought treatment at our institution between January 2021 and January 2025. The cohort was divided into two groups based on the treatment regimen they received: the observation group (n=189), which comprised patients treated with SGLT2 inhibitors, and the control group (n=161), which included patients treated with other antidiabetic therapies who did not receive SGLT2 inhibitors. The study aimed to evaluate the potential impact of SGLT2 inhibitors on tumor development risk in patients with diabetes.

Patients were accepted into the study if they had type 2 diabetes certified by the American Diabetes Association,[12] were followed at our institution for at least one year and agreed to take part by signing a consent form. All the included patients were at least 18 years old and their medical records had to be complete and accessible, with information on their health and treatment. Patients who received empagliflozin, dapagliflozin or canagliflozin formed the observation group and those who took metformin, sulfonylureas, insulin or GLP-1 receptor agonists (but not SGLT2 inhibitors) were in the control group. Exclusion criteria were as follows: a diagnosis of type 1 diabetes or any other secondary form of diabetes, active malignancy or a history of cancer within the past five years (except non-melanoma skin cancer), severe comorbidities such as advanced cardiovascular disease, chronic kidney disease with an eGFR <30 mL/min/1.73m^2, or hepatic cirrhosis. People diagnosed with major psychiatric conditions, those with cognitive impairments and those who were pregnant or breastfeeding were not included in the trial. In addition, patients who had previously experienced sensitivity or allergic reactions to SGLT2 inhibitors were not allowed in the study. The goal was to check if receiving SGLT2 inhibitors could affect cancer risk and to do this by comparing cancer incidence in the two groups, taking into account age, gender, the length of diabetes and presence of other health problems.

The observation group (n=189) consisted of patients who were treated with SGLT2 inhibitors, including empagliflozin, dapagliflozin, or canagliflozin, as part of their diabetes management. These patients received regular follow-up visits and were monitored for any adverse effects as well as cancer incidence. The control group (n=161) included patients who were treated with other standard antidiabetic therapies, such as metformin, sulfonylureas, insulin, or glucagon-like peptide-1 (GLP-1) receptor agonists, but did not receive SGLT2 inhibitors.

Intervention Methods and Data Collection

In the observation group (n=189), patients were treated with one of three SGLT2 inhibitors: empagliflozin, dapagliflozin, or canagliflozin, with the distribution of these drugs being 35%, 40%, and 25%, respectively. Empagliflozin was administered at a dose of 10 mg once daily, with the dose increased to 25 mg once daily if needed for optimal glycemic control. Dapagliflozin was prescribed at 10 mg once daily, with a possible increase to 20 mg once daily based on the patient's clinical response. Canagliflozin was given at an initial dose of 100 mg once daily, which could be increased to 300 mg once daily if tolerated and required. All doses were adjusted according to the patient's individual needs and response to treatment. In the control group (n=161), patients received standard antidiabetic treatments, including

metformin, sulfonylureas, insulin, and GLP-1 receptor agonists. Metformin was prescribed at a starting dose of 500 mg once or twice daily, with the dose increased up to 2000–2500 mg per day depending on tolerance. Sulfonylureas were given at doses ranging from 5 mg to 20 mg per day, depending on the specific agent used and the patient's blood glucose control. Insulin therapy, including both basal and bolus insulin, was prescribed based on the patient's individual needs, typically starting with 10–20 units per day and adjusted based on blood glucose levels. GLP-1 receptor agonists were administered at doses starting from 0.6 mg once weekly, with potential increases based on patient response and tolerability, up to 1.8 mg weekly.

Outcome Measurement

The primary outcome was the incidence of malignant tumors, including lung, ovarian, colorectal, prostate, breast, pancreatic, bladder, kidney, esophageal, and hepatocellular cancers, identified through medical and pathological records. Secondary outcomes encompassed metabolic indicators (FBG, HbA1c, insulin, C-peptide, lipids), hepatic and renal function parameters (ALT, AST, BUN, eGFR, creatinine), and survival endpoints. Tumor incidence and subtype distribution were compared between the SGLT2 inhibitor and control groups, while subgroup analyses examined the influence of smoking, alcohol consumption, and diabetes control. Progression-free and overall survival were evaluated using Kaplan–Meier analysis with Log rank testing. These outcomes were designed to comprehensively determine whether SGLT2 inhibitor therapy reduces tumor risk—particularly for lung and ovarian cancers—while improving metabolic control, renal function, and long-term survival in patients with type 2 diabetes.

Statistical Methods

All analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., USA). Continuous variables were expressed as mean ± SD and compared with independent t-tests; categorical variables were analyzed with chi-square or Fisher's exact tests. Logistic regression was applied to evaluate tumor incidence between groups, adjusting for age, sex, BMI, smoking, and diabetes duration. Subgroup comparisons were conducted for smoking, alcohol use, and diabetes control. Changes in metabolic, hepatic, and renal indicators were analyzed with t-tests. Progression-free and overall survival were estimated using Kaplan–Meier curves and compared by the Log rank test. All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Baseline Characteristics of Patients

Age (P = 0.280), sex distribution (P = 0.557), and diabetes duration (P = 0.059) were similar, indicating adequate group matching. Indicators of metabolic status, including BMI (P = 0.156), hypertension (P = 0.116), and hyperlipidemia (P = 0.816), showed no meaningful variation. Lifestyle factors such as smoking and alcohol consumption were evenly distributed (P = 0.842 and P = 0.780, respectively). Likewise, family history of diabetes (P = 0.864), comorbid cardiovascular (P = 0.667) and renal diseases (P = 0.759) did not differ significantly. The use of antidiabetic therapies—including metformin, sulfonylureas, insulin, DPP-4 inhibitors, and GLP-1 receptor agonists—was also comparable (all P > 0.05) (Table 1). Collectively, these data confirm that the two cohorts were well balanced at baseline, minimizing potential confounding and ensuring the validity of subsequent outcome comparisons.

Compare Incidence of Tumor Development Between Two Groups

Overall tumor incidence was significantly lower in the observation group than in the control group (P < 0.001). In subtype analyses, the observation group showed markedly fewer cases of lung cancer (P = 0.018) and ovarian cancer (P = 0.017). Differences for other malignancies were not statistically significant, including breast (P = 0.843), colorectal (P = 0.071), prostate (P = 0.071), pancreatic (P = 0.658), bladder (P = 0.306), kidney (P = 0.471), esophageal (P = 0.306), and hepatocellular carcinoma (P = 0.909) (Table 2). Collectively, these data indicate a robust reduction in overall tumor risk, driven primarily by lower incidences of lung and ovarian cancers in the observation group.

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Table 1 Baseline Characteristics of Patients

Characteristic	Observation Group (n=189)	Control Group (n=161)	P-Value
Age (years)	58.04±10.24	59.24±10.33	0.280
Gender (Male)			0.557
Male	108	97	
Female	81	64	
Diabetes Duration (years)	9.32±2.28	9.80±2.43	0.059
BMI (kg/m^2)	24.92±3.21	24.17±6.34	0.156
Hypertension (Cases)	136	113	0.715
Hyperlipidemia (Cases)	121	105	0.816
Smoking (Cases)	38	31	0.842
Alcohol Consumption (Cases)	28	27	0.780
Family History of Diabetes (Cases)	98	82	0.864
Comorbid Cardiovascular Disease (Cases)	57	52	0.667
Comorbid Renal Disease (Cases)	26	24	0.759
Diabetes Medication Use			
Metformin(Cases)	161	142	0.410
Sulfonylureas	79	63	0.612
Insulin(Cases)	53	48	0.715
DPP-4 Inhibitors(Cases)	62	50	0.727
GLP-1 Agonists(Cases)	28	23	0.889

Abbreviations: DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide-1.

Table 2 Compare Incidence of Tumor Development Between Two Groups

Tumor Type	Observation Group (n=189)	Control Group (n=161)	P-Value
Overall Tumor Incidence	23	51	<0.001
Lung Cancer	5	13	0.018
Breast Cancer	3	3	0.843
Colorectal Cancer	3	8	0.071
Prostate Cancer	3	8	0.071
Pancreatic Cancer	2	1	0.658
Bladder Cancer	2	4	0.306
Kidney Cancer	1	2	0.471
Ovarian Cancer	1	7	0.017
Esophageal Cancer	2	4	0.306
Hepatocellular Carcinoma	1	1	0.909

Smoking, Alcohol Consumption, and Tumor Development

Compared with non-smokers, smokers exhibited a higher overall tumor incidence (51 vs 23; P<0.001). Site-specific excesses among smokers were evident for lung cancer (P=0.019) and ovarian cancer (P=0.016), with borderline elevations for colorectal and prostate cancers (P=0.065 for both). Differences for other sites were not significant—breast (P=0.821), pancreatic (P=0.673), bladder (P=0.292), kidney (P=0.458), esophageal (P=0.292), and hepatocellular carcinoma (P=0.896). A similar pattern was observed for alcohol consumption: relative to non-consumers, consumers had higher overall tumor incidence (P<0.001) and significantly more lung (P=0.020) and ovarian cancers (P=0.016), with borderline differences for colorectal and prostate cancers (P=0.068 for both). Other sites again showed no significant differences—breast (P=0.832), pancreatic (P=0.666), bladder (P=0.299), kidney (P=0.464), esophageal (P=0.121), and hepatocellular carcinoma (P=0.903) (Table 3).

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Table 3 Smoking, Alcohol Consumption, and Tumor Development

Factor	Smoking (n=159)	Non-Smoking (n=191)	P-Value	Alcohol Consumption (n=160)	Non-Alcohol Consumption (n=190)	P-Value
Overall Tumor Incidence	51	23	<0.001	51	23	<0.001
Lung Cancer	13	5	0.019	13	5	0.020
Breast Cancer	3	3	0.821	3	3	0.832
Colorectal Cancer	8	3	0.065	8	3	0.068
Prostate Cancer	8	3	0.065	8	3	0.068
Pancreatic Cancer	1	2	0.673	1	2	0.666
Bladder Cancer	4	2	0.292	4	2	0.299
Kidney Cancer	2	1	0.458	2	1	0.464
Ovarian Cancer	7	1	0.016	7	1	0.016
Esophageal Cancer	4	2	0.292	4	2	0.121
Hepatocellular Carcinoma	1	1	0.896	1	1	0.903

Diabetes Control and Tumor Development Risk

Patients with uncontrolled diabetes had a higher overall tumor incidence than those with controlled diabetes (P<0.001). Site-specific differences favored the controlled group for lung cancer (P=0.023) and ovarian cancer (P=0.018). Other tumor types showed no statistically significant differences: breast (P=0.854), colorectal (P=0.074), prostate (P=0.074), pancreatic (P=0.651), bladder (P=0.313), kidney (P=0.477), esophageal (P=0.313), and hepatocellular carcinoma (P=0.916) (Table 4).

Compare the Blood Glucose and Lipid Indicators Between Two Groups

Observation group members had lower FBG and HbA1c values than people in the control group which means their blood sugar control was better with the SGLT2 inhibitor ($P < 0.001$ for each). In addition, it was found that both insulin levels and C-peptide concentrations which indicate insulin secretion, decreased in the observation group ($p = 0.03$ for insulin, $p = 0.04$ for C-peptide), pointing to enhanced insulin sensitivity. Lipid profile analysis also showed significant differences, with the observation group displaying lower levels of low-density lipoprotein (LDL) and total cholesterol (TC), and higher levels of high-density lipoprotein (HDL), as compared to the control group ($P < 0.05$ for LDL and HDL, $P < 0.001$ for TC). Triglyceride (TG) levels were also significantly reduced in the observation group ($P < 0.001$) (Figure 1). According to the results, SGLT2 inhibitors help control blood glucose and also improve the handling of lipids which is good for overall metabolic health.

Table 4 Diabetes Control and Tumor Development Risk

Tumor Type	Controlled Diabetes (n=188)	Uncontrolled Diabetes (n=162)	P-Value
Overall Tumor Incidence	23	51	<0.001
Lung Cancer	5	13	0.023
Breast Cancer	3	3	0.854
Colorectal Cancer	3	8	0.074
Prostate Cancer	3	8	0.074
Pancreatic Cancer	2	1	0.651
Bladder Cancer	2	4	0.313
Kidney Cancer	1	2	0.477
Ovarian Cancer	1	7	0.018
Esophageal Cancer	2	4	0.313
Hepatocellular Carcinoma	1	1	0.916

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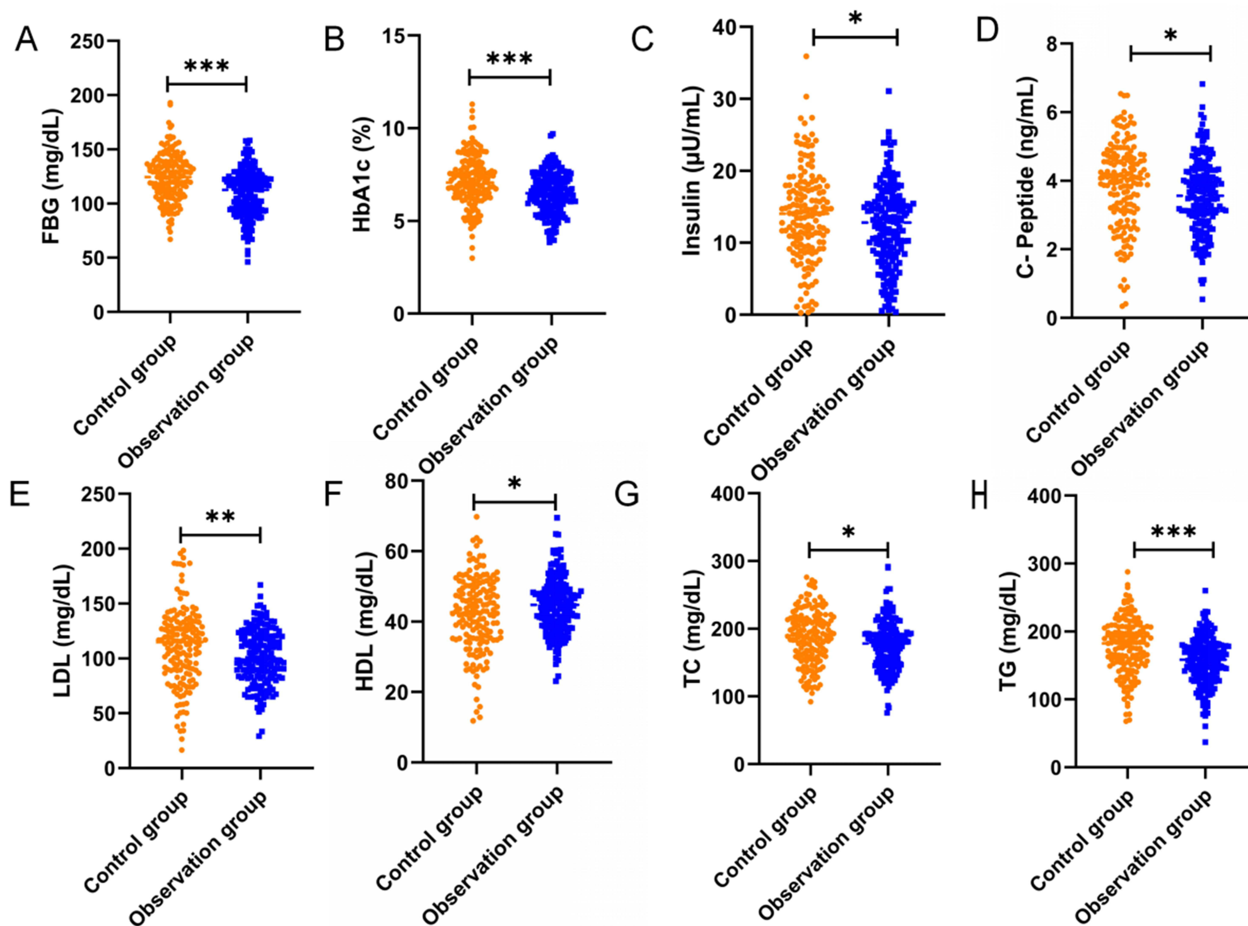

Figure 1 Compare the blood glucose and lipid indicators between two groups. (**A**) FBG, (**B**) HbA1c, (**C**) Insulin, (**D**) C-Peptide, (**E**) LDL, (**F**) HDL, (**G**) TC, (**H**) TG. Compare to the control group, *P<0.05, Compare to the control group, **P<0.01, Compare to the control group, ***P<0.001.

Abbreviations: FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1c; Insulin, Insulin (Endogenous); C-Peptide, C-Peptide (Insulin Secretion Marker); LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides.

Compare Liver and Kidney Function Indicators Between Two Groups

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels showed no significant differences between the two groups ($p = 0.47$ for ALT, $p = 0.21$ for AST), indicating that liver function was similarly maintained in both groups. However, blood urea nitrogen (BUN) levels were significantly lower in the observation group compared to the control group ($P < 0.001$), suggesting improved renal function with SGLT2 inhibitor treatment. Furthermore, estimated glomerular filtration rate (eGFR) was significantly higher in the observation group ($P < 0.001$), indicating better kidney function. Serum creatinine levels were also significantly reduced in the observation group ($P < 0.001$), further supporting the beneficial effects of SGLT2 inhibitors on kidney health (Figure 2). These findings suggest that SGLT2 inhibitors may have a positive impact on renal function without adversely affecting liver function.

Kaplan-Meier Survival Curves Comparing Progression-Free Survival and Overall Survival Between the Two Group

As shown in Figure 3A, the progression-free survival rate was significantly higher in the observation group compared to the control group ($P<0.01$), with the SGLT2 inhibitor treatment showing a prolonged time to progression. Similarly, the overall survival rate, depicted in Figure 3B, also favored the observation group, demonstrating a statistically significant improvement in survival compared to the control group ($P < 0.01$). These findings indicate that treatment with SGLT2

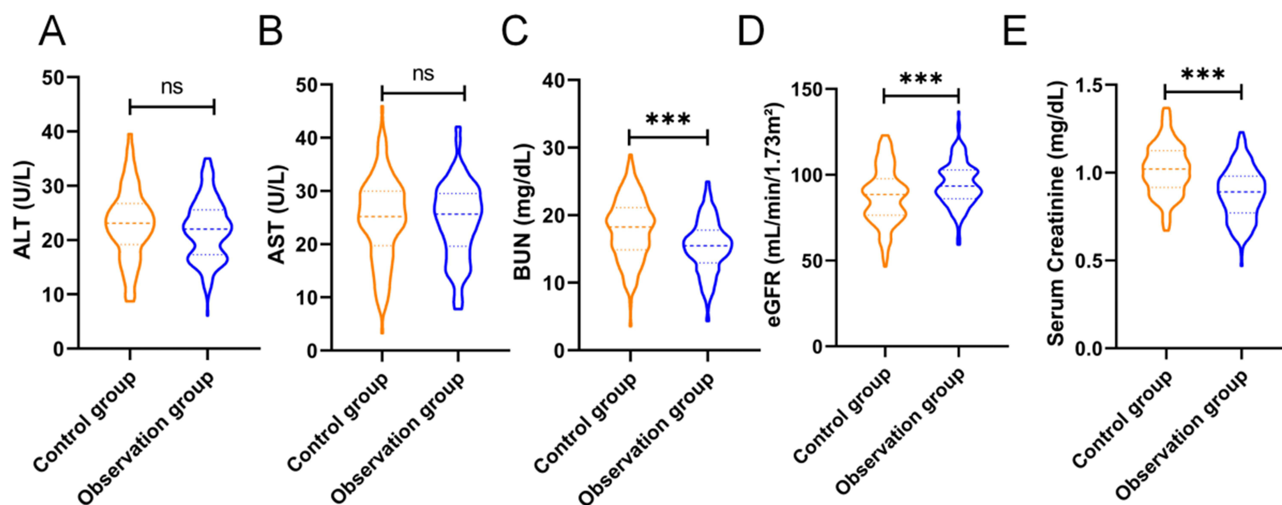

Figure 2 Compare liver and kidney function indicators between two groups. (**A**) ALT, (**B**) AST, (**C**) BUN, (**D**) eGFR, (**E**) Serum Creatinine. Compare to the control group, ***P<0.001.

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; eGFR Estimated Glomerular Filtration Rate.

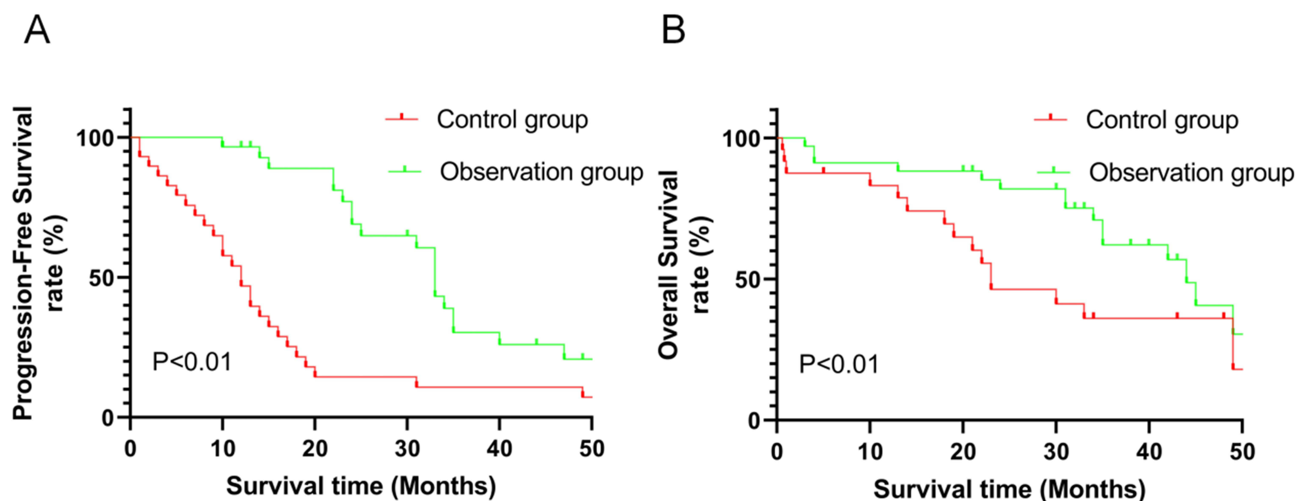

Figure 3 Kaplan-Meier survival curves comparing progression-free survival and overall survival between the two Group. (**A**) Progression-free survival, (**B**) overall survival.

inhibitors is associated with improved survival outcomes, both in terms of progression-free and overall survival, suggesting a potential benefit in cancer risk management among diabetic patients.

Discussion

The study analyzes in detail whether SGLT2 inhibitors affect the likelihood of tumors in patients with T2D. It appears that these drugs may guard against certain cancers, specifically lung cancer and may enhance overall metabolic health. In detail, SGLT2 inhibitors were linked to a lower rate of cancer overall, a lower risk of lung cancer and improvements in blood sugar and lipid levels. The study also points out that smoking and drinking alcohol can raise cancer risks and managing diabetes may cut the chance of developing tumors. However, as some findings are encouraging, more research is needed to fully understand what lies behind them and what their results might mean in the long run.

Data from the study indicates that SGLT2 inhibitors potentially lowers the chances of getting cancer, especially lung cancer. Other studies have suggested that SGLT2 inhibitors may have a role in fighting certain forms of cancer. One more study noted that people using SGLT2 inhibitors had a lower cancer risk as a group, even though the study did not examine lung cancer in the diabetic group.[10,13] It is possible that the drug we studied helped reduce lung cancer risk by

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increasing insulin sensitivity and reducing inflammation which are both mechanisms linked to cancer growth.[14,15] Finding a way to lower hyperinsulinemia could be one way to lower the risk of lung cancer progression and spread.

In contrast to the promising findings for lung cancer, the study also noted that SGLT2 inhibitors did not significantly affect the incidence of breast, prostate, or colorectal cancers. These results align with current study, which also found no significant reduction in the incidence of breast or prostate cancer in patients treated with SGLT2 inhibitors.[16,17] The lack of significant impact on these cancers may be attributed to the complex nature of cancer pathogenesis, where factors such as genetics, hormonal influences, and environmental exposures play a more prominent role. Additionally, the duration of exposure to SGLT2 inhibitors may not have been long enough to observe significant effects on these cancer types, as longer-term studies are needed.

Managing diabetes correctly is a main focus of this study when it comes to tumor development. We noticed that people with controlled diabetes have a lower risk of tumors which is in line with findings from others showing a link between lower cancer chances and good blood sugar control.[18] Taking care of diabetes well may play a role in cancer prevention, since too much insulin and glucose in the blood are associated with the growth of tumors.[19] Taking SGLT2 inhibitors may help lower blood sugar and improve resistance to insulin which can reduce the risk of cancer. However, other traits such as smoking and drinking alcohol might prevent the results of diabetes control from showing a difference for lung cancer.

The analysis of smoking and alcohol consumption further underscores the complex relationship between lifestyle factors and cancer risk. Smoking was found to be a significant risk factor for tumor development, particularly lung cancer, a finding consistent with the established literature on smoking and cancer. This aligns with studies that highlighted smoking as a major risk factor for lung cancer.[20,21] Similarly, alcohol consumption also showed significant associations with overall tumor risk, especially lung cancer. While smoking and alcohol are well-known carcinogens, the interaction between these lifestyle factors and diabetes treatment warrants further investigation.[22] It is possible that SGLT2 inhibitors may partially mitigate the harmful effects of these behaviors on cancer risk, but the potential benefit may be limited in the face of these modifiable risk factors.

Several issues arise that need to be mentioned here. Because the study is observational, it is impossible to say SGLT2 inhibitors increase the risk of cancer. Because the study followed the participants for only a short time, important long-term effects of SGLT2 inhibitors on cancer risk might not have been noticed. But even though the research used control variables, others, like natural genetic issues and the environment around patients, could have still affected the outcomes. Also, this investigation only considered patients with Type 2 Diabetes, so its findings may not fit people who do not have diabetes or other relevant conditions.

In summary, this study indicates that the use of SGLT2 inhibitors in patients with type 2 diabetes may be associated with a reduced risk of lung cancer and improved overall survival, suggesting potential benefits beyond glycemic control. However, these effects appear to be cancer-specific, as only lung cancer demonstrated a statistically significant reduction, while other tumor types showed no consistent associations. Given the retrospective design, moderate sample size, and relatively short four-year follow-up period, these findings should be regarded as preliminary rather than conclusive. Further large-scale, long-term prospective studies and randomized controlled trials are warranted to validate these associations and elucidate the underlying biological mechanisms. Clinically, while SGLT2 inhibitors remain important agents for improving metabolic, renal, and cardiovascular outcomes in diabetes management, clinicians should balance their potential anticancer benefits with possible risks when considering long-term treatment.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and the data supporting the findings of this study will be made available upon reasonable request to the corresponding author.

Ethical Approval Statement

This study was approved by the ethics committee of Qingdao Endocrine and Diabetes Hospital, No.2025031001. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Author Contributions

Yuzhe Wang, Yusen Ding: Conceptualization, Methodology, Software Zhen Li, Yamei Zhu, XiangLong Yan: Data curation, Writing- Original draft preparation, Writing – Review & Editing. Jia Yao: Visualization, Investigation, Writing- Original draft preparation, Writing – Review & Editing. Meiling Wang: Supervision, Software, Validation, Writing- Original draft preparation, Writing – Review & Editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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