JAMA Oncology | Original Investigation

GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity

Hao Dai, PhD; Yongqiu Li, MS; Yao An Lee, MS; Ying Lu, BA; Thomas J. George, MD; William T. Donahoo, MD; Kelvin P. Lee, MD; Harikrishna Nakshatri, PhD; John Allen, PharmD; Yi Guo, PhD; Ramon C. Sun, PhD; Jingchuan Guo, MD, PhD; Jiang Bian, PhD

IMPORTANCE Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely prescribed for glycemic control in type 2 diabetes and have recently gained popularity for weight management. However, their long-term impact on cancer risk remains uncertain. Understanding this association is crucial for patient safety.

OBJECTIVE To compare the incidence of 14 cancers among adults with obesity prescribed GLP-1RAs vs nonusers.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study followed a target trial emulation design using 2014 to 2024 electronic health record data from OneFlorida+, a multicenter health research network that integrates real-world clinical data from diverse health care settings. Adults 18 years or older eligible for antiobesity medications without prior cancer history were included. Participants were categorized as GLP-1RA users or nonusers, matched 1:1 using propensity scores.

EXPOSURE Individuals taking vs not taking GLP-1RAs.

MAIN OUTCOMES AND MEASURES The primary outcomes were the incidence of 14 cancer types, including 13 obesity-associated cancers (liver, thyroid, pancreatic, bladder, colorectal, kidney, breast, endometrial, meningioma, upper gastrointestinal, ovarian, multiple myeloma, and prostate) and lung cancer.

RESULTS A total of 86 632 matched adults (mean [SD] age, 52.4 [14.5] years; 68.2% female) were included, comprising 43 317 GLP-1RA users and 43 315 otherwise eligible nonusers. The incidence rates of the 14 cancers were 13.6 vs 16.4 per 1000 person-years, respectively, indicating a significantly lower overall cancer risk among individuals taking GLP-1RAs (hazard ratio [HR], 0.83 [95% CI, 0.76-0.91]; $P = .002$) compared with nonusers. In particular, taking GLP-1RAs was associated with a reduced risk of endometrial cancer (HR, 0.75 [95% CI, 0.57-0.99]; $P = .05$), ovarian cancer (HR, 0.53 [95% CI, 0.29-0.96]; $P = .04$), and meningioma (HR, 0.69 [95% CI, 0.48-0.97]; $P = .05$). However, GLP-1RAs were associated with a marginally nonsignificant increased risk of kidney cancer (HR, 1.38 [95% CI, 0.99-1.93]; $P = .04$).

CONCLUSIONS AND RELEVANCE This retrospective cohort study found that taking GLP-1RAs was associated with a reduced overall risk of cancer, including lower risks of endometrial, ovarian, and meningioma cancers, among patients with obesity or overweight. However, taking GLP-1RAs may be associated with an increased risk of kidney cancer, highlighting the need for longer-term follow-up to clarify the underlying mechanisms and clinical implications of these findings.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jiang Bian, PhD, Regenstrief Institute and Indiana University, 1101 W 10th St, Indianapolis, IN 46202 (bianji@iu.edu).

JAMA Oncol. doi:10.1001/jamaoncol.2025.2681
Published online August 21, 2025.

Obesity, characterized by excessive fat accumulation,[1] is a significant public health concern in the US.[2] As of 2021, more than 100 million US adults were living with obesity,[2] contributing to a growing burden of chronic diseases and rising health care costs.[3] Obesity significantly increases the risk of developing several serious conditions, including type 2 diabetes (T2D).[2] More critically, obesity is associated with at least 13 types of cancer,[2] which account for approximately 40% of all cancer diagnoses each year in the US.[4] As obesity rates continue to rise, identifying effective interventions to mitigate cancer risk among individuals with obesity is a critical public health priority.[5,6]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), a new class of antihyperglycemic agents, have emerged as a promising pharmacologic intervention for obesity and related comorbidities. Initially developed for T2D treatment, GLP-1RAs have demonstrated efficacy in promoting weight loss, leading to US Food and Drug Administration approval for chronic weight management in 2014.[7,8] Beyond their effects on glycemic control and weight loss, recent studies suggest GLP-1RAs may also influence cancer risk.[9-11]

Although these findings provide insight into the potential relationship between GLP-1RAs and cancer risk, all existing studies have focused on comparisons among glucose-lowering drugs (GLDs) in patients with T2D, leaving uncertainty regarding their potential role in cancer prevention in individuals with obesity regardless of diabetes status. Additionally, previous studies often did not address variation in treatment effects across different patient groups, known as heterogeneity of treatment effects (HTE). Factors such as age, sex, and baseline metabolic conditions may influence how GLP-1RAs affect cancer risk, possibly contributing to conflicting findings across international studies.[11,12] These discrepancies may be partially attributable to differences in study design, comparator selection, and confounding control, as well as variability in patient characteristics.

To better address these challenges, a target trial emulation study using real-world data from the OneFlorida+ Clinical Research Network was conducted. The study design followed a target trial emulation framework to minimize biases inherent in observational research, specifically aiming to reduce confounding and immortal time bias through the emulation of a randomized trial framework.[13,14] The incidence of 14 cancer types was compared between GLP-1RA users and nonusers among individuals with obesity and overweight who were eligible for antiobesity treatment. Specifically, 13 obesity-associated cancers were studied (liver, thyroid, pancreatic, bladder, colorectal, kidney, breast, endometrial, meningioma, upper gastrointestinal, ovarian, multiple myeloma, and prostate) and lung cancer. To further explore response variability, HTE and individualized treatment effect (ITE) analyses using advanced machine learning methods were incorporated to further identify subgroups of patients who may derive the maximal benefit or experience potential harm from GLP-1RA therapy in relation to cancer risk.[15]

Key Points

Question Is taking glucagon-like peptide-1 receptor agonists (GLP-1RAs) associated with the risk of developing cancer among adults with obesity?

Findings In this retrospective cohort study using a target trial emulation design with electronic health records from OneFlorida+, 43 317 individuals taking GLP-1RAs were compared with 43 315 matched nonusers. Taking GLP-1RAs was significantly associated with a reduced risk of overall cancer, particularly for endometrial, meningioma, and ovarian cancers; however, GLP-1RAs were associated with a nonsignificant increased risk of kidney cancer.

Meaning These findings suggest taking GLP-1RAs may influence cancer risk, highlighting the need for long-term follow-up to understand underlying mechanisms.

Methods

Study Design and Data Source

We conducted a target trial emulation (eTable 1 in Supplement 1) using a retrospective cohort study with a new-user design, applying a time-dependent propensity score–matching approach to balance baseline covariates between comparison groups, thereby mimicking randomization. An intention-to-treat analysis was conducted to investigate the association between GLP-1RAs and cancer risk among adults with overweight and obesity with and without T2D. This study was approved and exempted from patient consent by the University of Florida Institutional Review Board because it was a retrospective secondary analysis of existing electronic health record (EHR) data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Our study used real-world OneFlorida+ data, covering the period from 2014 to 2024. OneFlorida+ consists of 14 health care organizations and contains longitudinal patient-level EHRs for 20 million individuals from Florida, Georgia, and Alabama.

Study Population

The study included patients eligible for antiobesity medications (AOMs) between January 1, 2014, and January 31, 2024. According to a 2013 American Heart Association/American College of Cardiology/The Obesity Society guideline, which we applied to this study, AOM eligibility was defined as (1) having a recorded diagnosis of obesity (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] ≥30) or (2) a BMI of 27 to 29.9 with at least 1 weight-related comorbidity.[16] Patients were excluded if they were younger than 18 years, had an active malignant neoplasm, or were pregnant on the cohort entry date.

The exposure of interest was the initiation of GLP-1RA treatment (eg, liraglutide, semaglutide, and tirzepatide, identified using RxNorm identifiers) (eTable 2 in Supplement 1). The comparator group, defined as patients who did not initiate GLP-1RA therapy during the study period, was constructed by aligning nonusers to GLP-1RA users within a ±1-week window of the

initiation date to ensure temporal comparability of treatment assignment. The index date was the first GLP-1RA prescription date for users and the matched visit date for nonusers. Patients were excluded if they had no encounter in the year before the index date, had less than 30 days of follow-up, or had prior malignant neoplasms.

Study Outcomes and Follow-Up

The study outcomes included 13 obesity-associated cancers (liver, thyroid, pancreatic, bladder, colorectal, kidney, breast, endometrial, meningioma, upper gastrointestinal, ovarian, multiple myeloma, and prostate). Additionally, preclinical studies suggested that GLP-1RAs suppress lung cancer cell proliferation in vitro and in vivo,[17] and evidence from population observational studies also showed a lower lung cancer risk associated with GLP-1RAs.[18,19] Therefore, we also included lung cancer as a primary outcome. Outcomes were identified through 1 or more corresponding diagnosis codes in *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* or *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* (eTable 3 in Supplement 1). Patients were followed up from the index date until the earliest of the following events: occurrence of the cancer of interest; death; last observation; or to the end of the study period on January 31, 2024.

Covariates

Baseline covariates included demographics, comorbidities, medications, and laboratory values (eTable 4 in Supplement 1). Race and ethnicity data were extracted from EHRs to describe the study population and enable subgroup analyses if disparities were present. Race and ethnicity categories included Hispanic, non-Hispanic Black, non-Hispanic White, and other (eg, multiracial, Asian, Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native). Medication information was collected during the year before or on the index date and comorbidities were collected 3 years prior to the index date.

Statistical Analysis

We performed 1:1 time-dependent propensity score matching to balance baseline covariates between GLP-1RA users and nonusers (eMethods 1 in Supplement 1). We assessed balance via standardized mean differences and Cohen *d*, with a standardized mean difference less than 0.1 indicating negligible imbalance.[20] Cancer incidence rates were calculated, and Kaplan-Meier curves illustrated cumulative incidence per 1000 person-years. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% CIs by comparing GLP-1RA users vs nonusers. Proportion assumptions were examined for Cox models. Subgroup analyses were performed to assess potential effect modifications by age (≥65 vs <65 years), sex, race and ethnicity (Hispanic vs non-Hispanic Black vs non-Hispanic White vs other), T2D (T2D vs no T2D at baseline), obesity (overweight vs obese), and specific GLPs (specific GLP use vs nonuse, in terms of liraglutide, semaglutide, and tirzepatide). To assess robustness, we used a Fine-Gray subdistribution hazard model[21] to account for the competing risk of mortality.

ITE and HTE

We used doubly robust meta-learner[22] for ITE estimation. A logistic model estimated the propensity score for GLP-1RA use, while the XGBoost regression model[23] modeled cancer risk outcomes. To ensure unbiased estimation, we applied a triple cross-fitting strategy for ITE estimation and bootstrapping for hyperparameter tuning within each round (eMethods 2 in Supplement 1).

Absolute risk differences (RDs) with 95% CIs captured the average exposure effect, with negative ITEs indicating benefit and positive values indicating harm. Additionally, we conducted HTE analyses based on the ITEs to explore risk variation across subgroups, using SHAP (Shapley Additive Explanations) values[24] and interpretable decision tree.[25] *P* values were 2-sided, with $P < .05$ considered statistically significant. All analyses were conducted using Python (Python Software Foundation) and survival curves were produced using R version 4.4.1 (R Foundation).

Results

The patient selection process is presented in **Figure 1**. After propensity score matching, the final cohort included 86 632 adults (43 317 individuals taking GLP-1RAs and 43 315 matched nonusers). Baseline characteristics are detailed in eTable 4 and eFigure 1 in Supplement 1. Participants had a mean (SD) age of 52.4 (14.5) years, 68.2% were female, 44.2% were non-Hispanic White, 50.7% had T2D, and 48.3% had obesity (BMI ≥30).

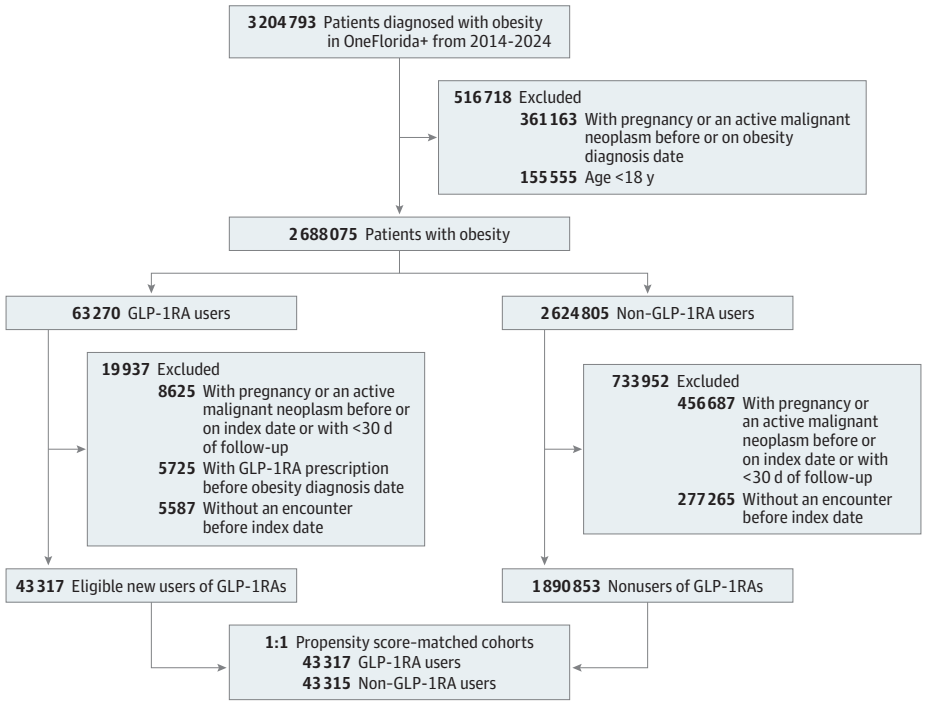
Figure 2 presents Kaplan-Meier plots showing the cumulative incidence of overall cancer during follow-up. Cumulative incidences for the individual 14 cancers are shown in eFigure 2 in Supplement 1. The IR of the 14 cancers was 13.6 per 1000 person-years for GLP-1RA users and 16.4 per 1000 person-years for GLP-1RA nonusers. The HR for overall cancer risk among GLP-1RA users vs nonusers was 0.83 (95% CI, 0.76-0.91; $P = .002$).

The forest plot for 14 cancer outcomes is shown in **Figure 3**. Specifically, taking GLP-1RAs was associated with a statistically significant decreased risk of endometrial cancer (HR, 0.75 [95% CI, 0.57-0.99]; $P = .05$), ovarian cancer (HR, 0.53 [95% CI, 0.29-0.96]; $P = .04$), and meningioma (HR, 0.69 [95% CI, 0.48-0.97]; $P = .05$). Notably, GLP-1RA use was associated with a nonsignificant trend toward increased risk of kidney cancer (HR, 1.38 [95% CI, 0.99-1.93]; $P = .04$). To evaluate the adequacy of our sample and guide future research, we performed a power and sample size projection analysis for endometrial, ovarian, and meningioma cancers (eTable 5 in Supplement 1).

Sensitivity and Subgroup Analyses

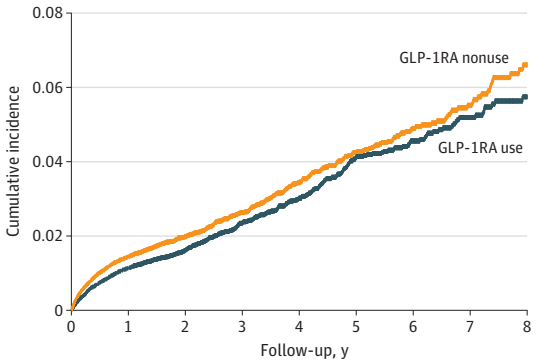
To account for competing risks, we conducted a Fine-Gray subdistribution hazard model, considering mortality as a competing event (eTable 6 in Supplement 1). These results rein-

Figure 1. Study Group Selection Flow Diagram



GLP-1RA indicates glucagon-like peptide-1 receptor agonist.

Figure 2. Cumulative Incidence of Overall Cancer in Patients Receiving Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) Compared With Patients Not Receiving GLP-1RAs



GLP-1RA use, No.									
At risk	43 317	42 713	19 908	9689	6000	3962	2496	1497	814
Censored	0	112	22 763	32 882	36 519	38 502	39 954	40 940	41 616
Events	0	492	646	746	798	853	867	880	887
GLP-1RA nonuse, No.									
At risk	43 315	42 509	18 763	9139	5489	3580	2169	1312	742
Censored	0	182	23 756	33 296	36 887	38 758	40 150	40 996	41 554
Events	0	624	796	880	939	977	996	1007	1019

forced the primary findings while ensuring robustness to competing risk considerations. Furthermore, we conducted a sensitivity analysis using a composite gynecologic cancer combining endometrial and ovarian cancer. The results (HR, 0.68 [95% CI, 0.52-0.87]) provided increased statistical power and strengthened the evidence. Additional post hoc analyses are presented in eResults 1 in Supplement 1. Results of subgroup analysis for 14 cancers can be seen in eFigure 3 in Supplement 1. GLP-1RA use was associated with a reduced risk for multiple cancer types across most subgroups, except for kidney cancer.

ITE and HTE Results

The details regarding data preprocessing and hyperparameter tuning are shown in eResults 2 in Supplement 1. Furthermore, the estimated RDs were negative for endometrial cancer (RD, −0.08% [95% CI, −1.22% to 1.07%]), ovarian cancer (RD, −0.03% [95% CI, −0.64% to 0.58%]), meningioma (RD, −0.05% [95% CI, −0.95% to 0.86%]), and gynecologic cancer (RD, −0.12% [95% CI, −1.33% to 1.08%]), suggesting potential benefits of GLP-1RAs for these cancers; the estimated RD for kidney cancer was 0.04% (95% CI, −0.70% to 0.77%), indicating a potential harm, although the CIs remained wide. All results were consistent with the Cox regression model. The ITE distributions are shown in eResults 3 in Supplement 1.

Interpretable Tree Analysis

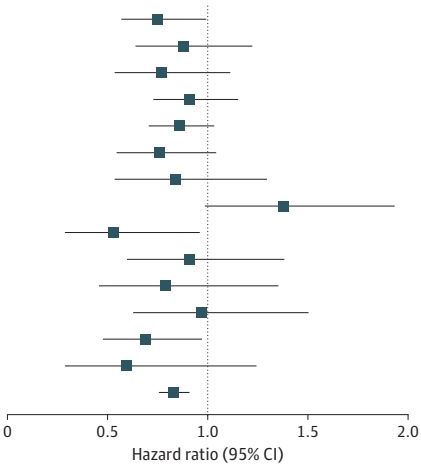
We used single decision tree models to identify patient subgroups with varying GLP-1RA effects. Detailed interpretable trees for endometrial, ovarian, meningioma, and kidney cancers are provided in eFigure 4A-D in Supplement 1.

Feature Importance for ITE Estimation

We applied SHAP values to identify the most influential features contributing to ITE variation. The top 10 predictors for each cancer highlighted critical clinical factors that may modify the impact of GLP-1RAs on cancer risk (eFigure 5A-D in Supplement 1). For example, baseline factors, such as heart failure, hospitalization for heart failure, metformin use, GLDs, insu-

Figure 3. Risk of 14 Cancers in Patients Receiving Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) Compared With Patients Not Receiving GLP-1RAs

Outcome	No./total No. (IR)		Hazard ratio (95% CI)
	GLP-1RA	Non-GLP-1RA	
Endometrial cancer	86/29 379 (2.93)	115/29 741 (3.87)	0.75 (0.57-0.99)
Colorectal cancer	70/43 317 (1.62)	76/43 315 (1.75)	0.88 (0.64-1.22)
Thyroid cancer	54/43 317 (1.25)	67/43 315 (1.55)	0.77 (0.54-1.11)
Prostate cancer	151/13 938 (10.91)	145/13 561 (10.69)	0.91 (0.73-1.15)
Breast cancer	200/29 379 (6.81)	234/29 741 (7.87)	0.86 (0.71-1.03)
Lung cancer	70/43 317 (1.62)	88/43 315 (2.03)	0.76 (0.55-1.04)
Pancreatic cancer	37/43 317 (0.85)	42/43 315 (0.97)	0.84 (0.54-1.30)
Kidney cancer	83/43 317 (1.92)	58/43 315 (1.34)	1.38 (0.99-1.93)
Ovarian cancer	17/29 379 (0.58)	32/29 741 (1.08)	0.53 (0.29-0.96)
Liver cancer	44/43 317 (1.02)	46/43 315 (1.06)	0.91 (0.60-1.38)
Multiple myeloma	24/43 317 (0.55)	29/43 315 (0.67)	0.79 (0.46-1.35)
Bladder cancer	41/43 317 (0.95)	40/43 315 (0.92)	0.97 (0.63-1.50)
Meningioma	55/43 317 (1.27)	76/43 315 (1.75)	0.69 (0.48-0.97)
Upper gastrointestinal cancer	12/43 317 (0.28)	19/43 315 (0.44)	0.60 (0.29-1.24)
Overall cancer	891/43 317 (20.5)	1022/43 315 (23.6)	0.83 (0.76-0.91)



IR indicates incidence rate.

lin, proton pump inhibitors, T2D, substance use, anticoagulant use, and hypertension, contributed most to the estimation of ITE for kidney cancer risk. The detailed SHAP results can be seen in eResults 4 in Supplement 1.

Feature Distribution Differences Between Benefit and Harm Groups

Based on the top 10 influential features, we examined their distributions across the relative benefit and relative harm groups. The results are shown in eResults 5 and eFigures 6 and 7 in Supplement 1.

Discussion

In this retrospective cohort study using data from the OneFlorida+ Clinical Research Network from 2014 to 2024, it was found that taking GLP-1RAs was associated with a significant reduction in overall cancer risk among adults with obesity or overweight, with or without T2D. Notably, significant risk reductions associated with GLP-1RA use were observed for ovarian, endometrial, and meningioma cancers. Although not statistically significant, a trend of risk reduction was noted for pancreatic, bladder, and breast cancers. However, GLP-1RA use appeared to be associated with an increased risk of kidney cancer, especially for those younger than 65 years or overweight (BMI 27-29.9).

Given that more than 137 million individuals in the US are currently eligible for GLP-1RA therapies, even modest changes in cancer risk could have substantial public health implications.[26] This study is one of the first to assess the association between GLP-1RA use and cancer risk in the broad, real-world population with obesity or overweight who are eligible for AOMs. Study findings align with previous work that only studied patients with T2D[11] and identified significant reductions in endometrial, ovarian, and meningioma cancers. These patterns raise the hypothesis that GLP-1RAs may be associated with a lower risk of hormone-sensitive malignant neoplasms.[27-29] Preclinical studies support the role of metabolic and hormonal pathways in endometrial cancer development. For instance, a study demonstrated that liraglutide inhibited the growth of Ishikawa endometrial cancer cells and promoted apoptosis (programmed cell death) in a dose-dependent manner.[30] Given that obesity and hyperinsulinemia are major risk factors for endometrial cancer, the metabolic effects of GLP-1RAs, particularly their role in weight loss and insulin sensitivity improvement, likely contribute to this association with reduced cancer risk.[30-33] Another preclinical study has shown that GLP-1RAs, such as exenatide, can inhibit the proliferation and invasion of ovarian cancer cells by downregulating metalloproteinases and upregulating their inhibitors. These findings suggest a potential functional role of GLP-1RAs in ovarian tissue and support their antitumor effect.[34] Given ovarian cancer is closely associated with obesity, hyperinsulinemia, and chronic inflammation,[35] it is also plausible that the metabolic improvements induced by GLP-1RAs contribute to reduced risk. In a survey of human tumors, approximately 35% of meningiomas were found to express measurable levels of GLP-1 receptors,[36] suggesting that meningioma cells may directly respond to GLP-1 or its analogs. GLP-1RAs significantly improve metabolic profiles, and given that meningiomas are known to exhibit hormone sensitivity,[37] these metabolic changes could plausibly influence tumor biology. However, direct evidence linking GLP-1RAs to a reduced risk of meningioma remains limited, aside from findings from a US observational study.[11] Further research is warranted to clarify these potential biological mechanisms specifically in the context of meningiomas.

For kidney cancer, the exploratory analysis indicated a marginally elevated risk associated with taking GLP-1RAs. This finding is consistent with a recent study, which reported a sig-

nificant increase in kidney cancer risk among individuals taking GLP-1RAs compared with metformin in patients with T2D.[11] GLP-1RAs have direct effects on kidney function mediated by GLP-1RAs in kidney vasculature; however, these are not associated with increased mitogenesis.[38] The biological mechanisms underlying a potential increased risk of kidney cancer remain unclear, especially given that GLP-1RAs have been shown to improve kidney function in other studies.[39,40] Further research is needed to clarify this potential risk.

HTE and Clinical Implications

Interpretable decision trees identified clinically relevant subgroups with potential differential responses to GLP-1RA therapy. For endometrial cancer, depression appeared to modify treatment response, with patients diagnosed with depression showing a modest association with reduced risk, while those without depression but taking oral corticosteroids did not benefit. These findings are consistent with literature linking depression, systemic inflammation, and metabolic dysregulation, suggesting possible neuroimmune mediation of GLP-1RA effects.[41,42] In meningioma, an association with reduced risk was observed among patients taking antidepressants, but not in those not taking antidepressants or not using proton pump inhibitors. Preclinical studies suggest that serotonergic antidepressants can directly affect tumor cell survival and the tumor microenvironment. Evidence indicates a potential antitumor effect through apoptosis induction,[43] inhibition of tumor growth via disruption of mitogenic pathways,[44] and immunomodulatory actions, such as reducing tumor-promoting inflammation and enhancing antitumor immune responses,[45] which may plausibly influence meningioma biology. Furthermore, the GLP-1 receptor and serotonin signaling pathways may interact synergistically. GLP-1RAs enhance central serotonin signaling, while selective serotonin reuptake inhibitors increase serotonin availability, potentially amplifying GLP-1–mediated effects.[46,47] For kidney cancer, depression was again associated with a potential protective signal, whereas substance use was linked to increased risk, implying a possible harmful interaction.

ITE Variability and Predictive Features

Study analysis also revealed that the efficacy of GLP-1RAs in cancer prevention may be influenced by individual clinical and metabolic factors. Regarding kidney cancer, a higher prevalence of insulin, metformin, and oral anticoagulant use, along with lower rates of substance use, was associated with reduced cancer risk among individuals taking GLP-1RAs. This finding aligns with research suggesting that taking certain substances is linked to an increased risk of kidney cancer,[48,49] while GLDs showed a potential association with reduced kidney cancer risk,[50] although strong evidence is still lacking.[51]

Limitations

This study has limitations. First, observational studies evaluating drug effects inherently carry risks of confounding by indication and unmeasured confounding. Notably, longitudinal assessments of BMI were not included. Thus, the study could not disentangle whether the observed cancer risk reduction was due to GLP-1RAs themselves or drug-induced weight loss. Additionally, glycemic control, another potential driver of cancer risk, was not evaluated longitudinally, restricting understanding of the role of GLP-1RA–induced glycemic improvement. Second, the performance of machine learning–based modeling heavily relies on data quality. Although cross-validation and bootstrapping techniques were used for model assessment and refinement, the incorporation of additional high-quality, longitudinal data could further enhance results. Third, the study focused exclusively on cancer-naive patients, and therefore, the findings may not generalize to populations with a previous cancer diagnosis or second cancer risk. Although the cohort was large, several cancer types had low event counts (such as ovarian and pancreatic cancers, which are generally low), resulting in wide CIs and limited statistical power. These findings should be interpreted with caution. Future studies with larger sample sizes are warranted to validate these associations. Fourth, tumorigenesis is often a prolonged process. Given the relatively recent approval and widespread uptake of GLP-1RAs, the study's follow-up duration may not have been sufficient to fully capture their long-term effects on cancer risk. This limitation, rooted in the underlying biology of cancer development, highlights the need for extended longitudinal follow-up in future research.

Conclusions

GLP-1RAs were associated with a reduced overall risk of cancer, including lower risks of endometrial cancer, ovarian cancer, and meningioma, among patients with obesity or overweight, regardless of T2D status. However, taking GLP-1RAs might be associated with an increased risk of kidney cancer, especially among patients younger than 65 years or those with overweight. These findings highlight the importance of tailored risk assessments and underscore the need for further long-term studies to clarify the impact of GLP-1RAs on cancer risk in high-risk populations.

ARTICLE INFORMATION

Accepted for Publication: May 19, 2025.

Published Online: August 21, 2025. doi:10.1001/jamaoncol.2025.2681

Author Affiliations: Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis (Dai, Bian); Department of Health Outcomes & Biomedical Informatics, College of Medicine, University of Florida, Gainesville (Li, Y. Guo); Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida, Gainesville (Y. A. Lee, Lu, J. Guo); Division of Hematology & Oncology, Department of Medicine, College of Medicine, University of Florida, Gainesville (George); Division of Endocrinology, Diabetes & Metabolism, College of Medicine, University of Florida, Gainesville (Donahoo); Melvin and Bren Simon Comprehensive Cancer Center, Indiana University, Indianapolis (K. P. Lee, Nakshatri, Bian); Department of Pharmacy Practice, College of Pharmacy, Purdue University, Indianapolis, Indiana (Allen); Department of Biochemistry and Molecular Biology, University of Florida, Gainesville (Sun); Center for Advanced Spatial Biomolecule Research, University of Florida, Gainesville (Sun); Regenstrief Institute, Indianapolis, Indiana (Bian).

Author Contributions: Mr Y. Lee and Dr J. Guo had full access to all of the data in the study and take

responsibility for the integrity of the data and the accuracy of the data analysis. Dr Dai and Ms Li equally contributed to the manuscript and serve as co–first authors.
Concept and design: Dai, Donahoo, Sun, J. Guo, Bian.
Acquisition, analysis, or interpretation of data: Dai, Li, Y. Lee, Lu, George, K. Lee, Nakshatri, Allen, Y. Guo, Bian.
Drafting of the manuscript: Dai, Li, Sun.
Critical review of the manuscript for important intellectual content: Dai, Y. Lee, Lu, George, Donahoo, K. Lee, Nakshatri, Allen, Y. Guo, Sun, J. Guo, Bian.
Statistical analysis: Dai, Y. Lee, Lu, Y. Guo.
Obtained funding: Sun, J. Guo, Bian.
Administrative, technical, or material support: Y. Lee, Lu, K. Lee, Allen, Bian.
Supervision: J. Guo, Bian.

Conflict of Interest Disclosures: Dr George reported serving on the data and safety monitoring boards of Seagen, Nihon Medi-Physics, KAHR Medical, and Arbele; consulting for Avammune Therapeutics, BillionToOne, Exact Sciences, and Summit Therapeutics; and receiving research support to his institution from Bristol Myers Squibb, Merck, AstraZeneca, Lilly, Bayer, Incyte, Ipsen, Genentech, Astellas Pharma, GlaxoSmithKline, Amgen, OncoC4, BillionToOne, Jounce Therapeutics, Elicio Therapeutics, AMAL Therapeutics/Boehringer Ingelheim, Seagen, Regeneron, and Deciphera. No other disclosures were reported.

Funding/Support: The study was supported by the National Institutes of Health's (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; R01DK133465).

Role of the Funder/Sponsor: The NIH and NIDDK had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: The study abstract was presented at the 2025 ASCO (American Society of Clinical Oncology) Annual Meeting; June 2, 2025; Chicago, Illinois.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Sung H, Siegel RL, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin*. 2019;69(2):88-112. doi:10.3322/caac.21499

2. CDC. Adult obesity facts. May 14, 2024. Accessed February 19, 2025. https://www.cdc.gov/obesity/adult-obesity-facts/index.html

3. Ward ZJ, Bleich SN, Long MW, Gortmaker SL. Association of body mass index with health care expenditures in the United States by age and sex. *PLoS One*. 2021;16(3):e0247307. doi:10.1371/journal.pone.0247307

4. CDC. Obesity and cancer. June 11, 2025. Accessed July 15, 2025. https://www.cdc.gov/cancer/risk-factors/obesity.html

5. Peralta M, Ramos M, Lipert A, Martins J, Marques A. Prevalence and trends of overweight and obesity in older adults from 10 European countries from 2005 to 2013. *Scand J Public Health*. 2018;46(5):522-529. doi:10.1177/1403494818764810

6. Henney AE, Wilding JPH, Alam U, Cuthbertson DJ. Obesity pharmacotherapy in older adults: a narrative review of evidence. *Int J Obes (Lond)*. 2025;49(3):369-380. doi:10.1038/s41366-024-01529-z

7. Apovian CM, Aronne LJ, Bessesen DH, et al; Endocrine Society. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415

8. Li H, Yu G, Huang Q, et al. Efficacy and safety of GLP-1RAs for people with obesity: a systematic review based on RCT and bayesian network meta-analysis. *Biomed Pharmacother*. 2024;171(116150):116150. doi:10.1016/j.biopha.2024.116150

9. Xie Y, Choi T, Al-Aly Z. Mapping the effectiveness and risks of GLP-1 receptor agonists. *Nat Med*. 2025;31(3):951-962. doi:10.1038/s41591-024-03412-w

10. Wang L, Wang Q, Li L, Kaelber DC, Xu R. GLP-1 receptor agonists and pancreatic cancer risk: target trial emulation using real-world data. *J Natl Cancer Inst*. 2025;117(3):476-485. doi:10.1093/jnci/djae260

11. Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Netw Open*. 2024;7(7):e2421305. doi:10.1001/jamanetworkopen.2024.21305

12. Bezin J, Gouverneur A, Pénichon M, et al. GLP-1 receptor agonists and the risk of thyroid cancer. *Diabetes Care*. 2023;46(2):384-390. doi:10.2337/dc22-1148

13. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254

14. Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. *JAMA*. 2022;328(24):2446-2447. doi:10.1001/jama.2022.21383

15. Varadhan R, Seeger JD. *Estimation and Reporting of Heterogeneity of Treatment Effects*. Agency for Healthcare Research and Quality; 2013.

16. Jensen MD, Ryan DH, Apovian CM, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023. doi:10.1016/j.jacc.2013.11.004

17. Pu Z, Yang Y, Qin S, Li X, Cui C, Chen W. The effect of liraglutide on lung cancer and its potential protective effect on high glucose-induced lung senescence and oxidative damage. *Front Biosci (Landmark Ed)*. 2023;28(10):259. doi:10.31083/j.fbl2810259

18. Wang J, Kim CH. Differential risk of cancer associated with glucagon-like peptide-1 receptor agonists: analysis of real-world databases. *Endocr Res*. 2022;47(1):18-25. doi:10.1080/07435800.2021.1955255

19. Song J, Cali Daylan AE, Chi KY, et al. Association between GLP-1 receptor agonists and incidence of lung cancer in treatment-naïve type 2 diabetes. *J Gen Intern Med*. 2025;40(4):973-976. doi:10.1007/s11606-024-09076-z

20. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med*. 2014;33(10):1685-1699. doi:10.1002/sim.6058

21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496. doi:10.1080/01621459.1999.10474144

22. Kennedy EH. Towards optimal doubly robust estimation of heterogeneous causal effects. *Electron J Stat*. 2023;17(2). doi:10.1214/23-EJS2157

23. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. arXiv. Revised June 10, 2016. Accessed July 15, 2025. http://arxiv.org/abs/1603.02754

24. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. In: Proceedings of the 31st International Conference on Neural Information Processing Systems. Curran Associates; 2017:4768-4777.

25. Tang H, Guo J, Shaaban CE, et al. Heterogeneous treatment effects of metformin on risk of dementia in patients with type 2 diabetes: a longitudinal observational study. *Alzheimers Dement*. 2024;20(2):975-985. doi:10.1002/alz.13480

26. Shi I, Khan SS, Yeh RW, Ho JE, Dahabreh IJ, Kazi DS. Semaglutide eligibility across all current indications for US adults. *JAMA Cardiol*. 2025;10(1):96-98. doi:10.1001/jamacardio.2024.4657

27. Ahmed M, Mäkinen VP, Mulugeta A, et al. Considering hormone-sensitive cancers as a single disease in the UK Biobank reveals shared aetiology. *Commun Biol*. 2022;5(1):614. doi:10.1038/s42003-022-03554-y

28. Agopiantz M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone receptor expression in meningiomas: a systematic review. *Cancers (Basel)*. 2023;15(3):980. doi:10.3390/cancers15030980

29. Wahab M, Al-Azzawi F. Meningioma and hormonal influences. *Climacteric*. 2003;6(4):285-292. doi:10.1080/cmt.6.4.285.292

30. Kanda R, Hiraike H, Wada-Hiraike O, et al. Expression of the glucagon-like peptide-1 receptor and its role in regulating autophagy in endometrial cancer. *BMC Cancer*. 2018;18(1):657. doi:10.1186/s12885-018-4570-8

31. Krause DD, Rai R, Benbrook DM, Chandra V. Effect of GLP-1 receptor agonist therapy in endometrial cancer. In: SGO 2024 Winter Meeting. Olympic Valley; 2024.

32. Kanda R, Hiraike H, Wada-Hiraike O, et al. Expression of the glucagon-like peptide-1 receptor and its role in regulating autophagy in endometrial cancer. *BMC Cancer*. 2018;18(1):657. doi:10.1186/s12885-018-4570-8

33. Riedinger CJ, Sakach J, Maples JM, et al. Glucagon-like peptide-1 (GLP-1) receptor agonists for weight management: a review for the gynecologic oncologist. *Gynecol Oncol*. 2024;190:1-10. doi:10.1016/j.ygyno.2024.07.008

34. He W, Yu S, Wang L, et al. Exendin-4 inhibits growth and augments apoptosis of ovarian cancer cells. *Mol Cell Endocrinol*. 2016;436:240-249. doi:10.1016/j.mce.2016.07.032

35. Zhang AMY, Wellberg EA, Kopp JL, Johnson JD. Hyperinsulinemia in obesity, inflammation, and cancer. *Diabetes Metab J*. 2021;45(3):285-311. doi:10.4093/dmj.2020.0250

36. Körner M, Christ E, Wild D, Reubi JC. Glucagon-like peptide-1 receptor overexpression in cancer and its impact on clinical applications. *Front Endocrinol (Lausanne)*. 2012;3:158. doi:10.3389/fendo.2012.00158

37. Seliger C, Meier CR, Becker C, et al. Metabolic syndrome in relation to risk of meningioma. *Oncotarget*. 2017;8(2):2284-2292. doi:10.18632/oncotarget.13667

38. Hviid AVR, Sørensen CM. Glucagon-like peptide-1 receptors in the kidney: impact on renal autoregulation. *Am J Physiol Renal Physiol*. 2020;318(2):F443-F454. doi:10.1152/ajprenal.00280.2019

39. Triozzi JL, Yu Z, Giri A, et al; VA Million Veteran Program. GLP1R gene expression and kidney disease progression. *JAMA Netw Open*. 2024;7(10):e2440286. doi:10.1001/jamanetworkopen.2024.40286

40. Badve SV, Bilal A, Lee MMY, et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2025;13(1):15-28. doi:10.1016/S2213-8587(24)00271-7

41. Bourou MZ, Matsas A, Valsamakis G, Vlahos N, Panoskaltsis T. The potential role of glucagon-like peptide-1 (GLP-1) receptor agonists as a type of conservative treatment of endometrial cancer in women of reproductive age: a review of the literature and a call for study. *Cureus*. 2024;16(9):e69678. doi:10.7759/cureus.69678

42. Leslie KK, Hagemann A, Thiel K, et al. The combination of the glucagon like peptide-1 receptor agonist semaglutide and the progestin levonorgestrel is highly effective in preclinical studies of endometrial cancer. American Association for Cancer Research. March 1, 2024. Accessed July 15, 2025. https://aacrjournals.org/clincancerres/article/30/5_Supplement/PR003/734739/Abstract-PR003-The-combination-of-the-glucagon

43. Kohli KM, Loewenstern J, Kessler RA, et al. Antidepressant use in patients with meningioma: is there an association with tumor recurrence? *Neurosurg Focus*. 2018;44(6):E14. doi:10.3171/2018.3.FOCUS17797

44. Knabbe J, Kowalski T, Seliger C. Pharmacological treatment of depression in patients with brain tumors. *Int J Cancer*. 2024;155(9):1533-1543. doi:10.1002/ijc.35058

45. Chen L, Huang S, Wu X, He W, Song M. Serotonin signalling in cancer: emerging mechanisms and therapeutic opportunities. *Clin Transl Med*. 2024;14(7):e1750. doi:10.1002/ctm2.1750

46. Anderberg RH, Richard JE, Eerola K, et al. Glucagon-like peptide 1 and its analogs act in the dorsal raphe and modulate central serotonin to reduce appetite and body weight. *Diabetes*. 2017;66(4):1062-1073. doi:10.2337/db16-0755

47. López-Ojeda W, Hurley RA. Glucagon-like peptide 1: an introduction and possible implications for neuropsychiatry. *J Neuropsychiatry Clin Neurosci*. 2024;36(2):A4-A86. doi:10.1176/appi.neuropsych.20230226

48. Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies. *Int J Cancer*. 2014;134(2):384-396. doi:10.1002/ijc.28093

49. Karami S, Daughtery SE, Schwartz K, et al. Analgesic use and risk of renal cell carcinoma: a case-control, cohort and meta-analytic assessment. *Int J Cancer*. 2016;139(3):584-592. doi:10.1002/ijc.30108

50. Tseng CH. Use of metformin and risk of kidney cancer in patients with type 2 diabetes. *Eur J Cancer*. 2016;52:19-25. doi:10.1016/j.ejca.2015.09.027

51. Nayan M, Punjani N, Juurlink DN, et al. Metformin use and kidney cancer survival outcomes: a systematic review and meta-analysis. *Am J Clin Oncol*. 2019;42(3):275-284. doi:10.1097/COC.0000000000000512