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ORIGINAL ARTICLE

GLP-1 receptor agonist use and cancer risk in obese nondiabetic adults

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Background: Recent data show that glucagon-like peptide-1 receptor agonist (GLP-1RA) use is associated with decreased cancer incidence in diabetic and obese patients. However, there have been no studies exclusively investigating the association of obesity-associated cancer (OAC) risks and GLP-1RAs in obese, nondiabetic patients.

Patients and methods: We conducted a target trial emulation to evaluate the association between GLP-1RA use and risk of 13 OACs. Using TriNetX, a nationwide database of 113 million US patients, we identified obese, nondiabetic adults without prior OAC diagnosis from December 2014 to June 2025. Patients prescribed GLP-1RAs were 1:1 propensity score matched to those receiving diet or exercise counseling and validated using inverse probability of treatment weighting. The primary outcome compared the cumulative incidence of OACs among treatment groups. The secondary outcome analyzed cancer incidence across sex (female, male), body mass index (<40, ≥ 40 kg/m^2), race (white, black), and drug (semaglutide, tirzepatide).

Results: The cohort included 229 467 patients; 86 422 (37.7%) received GLP-1RAs, while 143 045 (62.3%) received diet or exercise consultation. After 1:1 propensity score matching, the study cohort included 161 798 patients: 80 899 GLP-1RA users versus 80 899 patients on diet or exercise consultation. Mean age of patients was 47.2 years (standard deviation 14.8). With a median follow-up of 2 years (interquartile range 1-2 years), the propensity score matching analysis showed a significantly lower incidence of any OACs among GLP-1RA users (hazard ratio 0.59, 95% confidence interval 0.53-0.67). Secondary analyses showed that in all subgroups, except for black race, GLP-1RA use was associated with a lower cumulative incidence of OACs. The inverse probability of treatment weighting analysis confirmed the findings.

Conclusions: GLP-1RA use was associated with a significantly lower short-term incidence of OACs among obese, nondiabetic patients, with consistent results observed in subgroups, except for race. Prospective trials are needed to confirm causality.

Key words: cancer incidence, GLP-1 receptor agonists, obesity, obesity-associated cancers, pharmacoepidemiology

INTRODUCTION

By 2050, projections indicate that two-thirds of adults across the United States will be obese.[1] There are 13 human malignancies associated with obesity and are identified as obesity-associated cancers (OACs).[2] Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for the treatment of type 2 diabetes, have emerged as a transformative class of agents in obesity management.[3,4] In the United States, GLP-1RA use among obese, nondiabetic individuals increased from ~21 000 patients in 2019 to >174 000 in 2023.[5] Individuals receiving GLP-1RAs for obesity differ substantially from those treated for diabetes, with the obesity-treated population being younger and less burdened by metabolic comorbidities.[6-11]

Preclinical studies indicate that GLP-1 receptor activation suppresses proliferation and viability in cancer cells expressing native GLP-1 receptors.[12] In parallel, emerging observational evidence suggests that GLP-1RA use may be associated with reduced risk of selected OACs among

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individuals with diabetes or obesity, independent of glycemic status.[13,14] Whether this association extends to obese, nondiabetic patients is unknown.

To date, no study has specifically examined the association of GLP-1RA use and cancer risks in obese, nondiabetic patients. In this study, we emulated a target trial using a population-based database to compare the incidence of 13 OACs among obese, nondiabetic patients initiating GLP-1RA therapy for weight management and those receiving diet or exercise counseling.

PATIENTS AND METHODS

Study design and data source

The study is a population-based cohort designed within a target trial emulation framework (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2026.04.013). This approach applies trial-like eligibility and exclusion criteria.[15] Nonrandomized treatment assignment was addressed using two complementary approaches: propensity score matching, estimating the average treatment effect among treated individuals, and inverse probability of treatment weighting (IPTW), estimating the average treatment effect in the full cohort.[16-18] We utilized the TriNetX Research Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information), from ~113 million individuals, sourced from 64 health care institutions across 50 US states.[19] The dataset encompassed patient demographics, including age, race, ethnicity, socioeconomic status, insurance coverage, diagnosis codes, and drug information. The institutional review board (IRB) at our institution determined that the study did not constitute Human Subjects Research and was therefore exempt from IRB approval. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study population (eligibility criteria and treatment strategies)

We included obese adults with no prior diagnosis of diabetes, or any OAC, and had visits recorded in health care systems from 23 December 2014 through 18 June 2025. We selected this starting time point because the first GLP-1RA gained US Food and Drug Administration approval for chronic obesity management on 23 December 2014. Obesity was defined as a body mass index (BMI, weight in kilograms divided by square of height in meters) of at least 30 kg/m^2. *International Classification of Diseases* (ICD) codes for BMI $\geq$50 kg/m^2 were not included in the analysis because the TriNetX platform deemed these data to constitute sensitive information. The nondiabetic population was defined by excluding individuals with an ICD-10 diagnosis of diabetes or with prescriptions for insulin or metformin. Patients with BMI $<$30 kg/m^2 were also excluded. These inclusion and exclusion criteria were ascertained using ICD codes recorded in the 30 days preceding the index date to avoid misclassification bias. Patients with incomplete demographic data were excluded from the analysis.

The treatment strategies compared were initiation of GLP-1RA therapy versus initiation of diet or exercise consultation. Patients were classified as GLP-1RA users if they had $\geq$2 prescriptions.[20] Diet or exercise consultation served as the comparator, reflecting the recommended lifestyle management for this condition.[21] Individuals who pursue diet or exercise consultation are more comparable to GLP-1RA users with respect to health care utilization and motivation to reduce obesity-related risk. In contrast, comparisons with nonusers of GLP-1RAs would be more susceptible to healthy-user bias and confounding by indication, potentially leading to overestimation of associations.[22] Patients with both GLP-1RAs and diet/exercise consultation were excluded. We conducted a complete-case analysis by excluding observations with missing data. Specific clinical codes corresponding to inclusion criteria, treatment variables, endpoints, and covariates appear in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2026.04.013.

Study outcomes and follow-up

The primary outcome was time to develop any of the OACs, analyzed as cumulative incidence, comparing patients initiating GLP-1RA therapy with those receiving diet or exercise consultation. The composite outcome reflects the International Agency for Research on Cancer-defined OAC spectrum and was selected to maximize power for detecting early incidence differences rather than to imply shared biological mechanisms.[2] Secondary outcomes included analyses across subgroups defined by sex (female, male), baseline BMI ($<$40, $\geq$40 kg/m^2), race (black, white), and drug (semaglutide, tirzepatide). Semaglutide and tirzepatide were selected because they are the most used GLP-1RAs in obesity management.[23] In addition, site-specific outcomes were evaluated for each individual cancer and are included in the Supplementary data, available at https://doi.org/10.1016/j.annonc.2026.04.013. The occurrence of the 13 OACs was identified with ICD codes and included breast, colorectal, endometrial, kidney, pancreatic, thyroid, ovarian, esophageal, gastric, liver, and gallbladder cancers, multiple myeloma, and meningioma.[2] Eligible participants entered follow-up at the index date (first prescription of GLP-1RA, diet or exercise consultation between December 2014 and June 2025) and were observed until the earliest occurrence of the incident cancer, death, loss to follow-up, or 2 years after the index date. A 2-year follow-up window was selected because cases in the treatment group had median follow-up of 2 years, and this was in alignment with the findings from IQVIA National Prescription Audit, which showed that widespread acceptance of GLP-1RAs for obesity management did not significantly increase until mid-2023.[23] Accordingly, the study was designed to assess short-term cancer incidence rather than long-term cancer prevention effects.

Statistical analysis

Continuous data are presented as mean with standard deviation (SD), while categorical data are summarized as counts and percentages. The probability of treatment assignment was estimated using logistic regression with relevant baseline covariates that could have influenced treatment decisions. The covariates included demographic characteristics (age, sex, race, and ethnic group), comorbid conditions (hypertension, hyperlipidemia, depression, overweight/BMI status, family/personal history of cancer, history of long-term drug use, documented statin usage, diagnosis of genetic susceptibility to cancer, history of screening for cancer, smoking/alcohol use, socioeconomic/psychosocial status, and history of bariatric surgery). A detailed list of the covariates is shown in Table 1. Baseline covariates were assessed during the 30 days preceding initiation of the index treatment. Propensity score matching was carried out using a 1:1 greedy nearest-neighbor approach, with each subject matched once and without replacement and applying a caliper width set of 0.1 of the SD of the logit-transformed propensity score.[24] In addition, we applied IPTW to retain the entire treatment-comparison cohort by weighing each patient according to their propensity score to evaluate the robustness of the effect estimates.[16,17]

The causal association estimated corresponds to the intention-to-treat approach, reflecting outcomes based on initial assignments to the treatment strategies. Time-to-event comparisons employed Cox proportional hazards models to estimate daily event rates, yielding hazard ratios (HRs) with 95% confidence intervals (CIs), while cumulative

Table 1. Characteristics of patients who had diet or exercise consultation or GLP-1 receptor agonist, before and after propensity score matching

Characteristic	Before propensity score matching			After propensity score matching		
	Dietary or exercise consultation (N = 143 045)	GLP-1 receptor agonist (N = 86 422)	SMD	Dietary or exercise consultation (N = 80 899)	GLP-1 receptor agonist No. (%) (n = 80 899)	SMD
Age, years, mean (SD)	46.8 (15.7)	47.7 (13.1)	−0.06	47.3 (14.9)	47.0 (13.1)	0.015
Female	100 427 (70.2)	64 388 (74.5)	−0.10	60 123 (74.3)	60 066 (74.2)	0.002
Male	42 618 (29.8)	22 034 (25.5)	0.10	20 776 (25.7)	20 833 (25.8)	−0.002
Race						
American Indian or Alaska Native	857 (0.6)	340 (0.4)	0.03	286 (0.4)	337 (0.4)	−0.01
Asian	2291 (1.6)	1489 (1.7)	−0.01	1432 (1.8)	1462 (1.8)	−0.003
Black or African American	25 639 (17.9)	12 896 (14.9)	0.08	12 633 (15.6)	12 671 (15.7)	−0.001
Native Hawaiian or other Pacific Islander	1310 (0.9)	451 (0.5)	0.05	443 (0.5)	451 (0.6)	−0.001
Other race	5474 (3.8)	1523 (1.8)	0.12	1585 (2)	1519 (1.9)	0.006
Unknown	10 661 (7.5)	3412 (3.9)	0.15	3402 (4.2)	3409 (4.2)	0
White	96 813 (67.7)	66 311 (76.7)	−0.20	61 118 (75.5)	61 050 (75.5)	0.002
Ethnicity						
Hispanic or Latino	24 600 (17.2)	5562 (6.4)	0.32	5548 (6.9)	5559 (6.9)	−0.001
Not Hispanic or Latino	85 872 (60)	61 688 (71.4)	−0.24	57 963 (71.6)	56 798 (70.2)	0.03
Unknown	32 573 (22.8)	19 172 (22.2)	0.01	17 388 (21.5)	18 542 (22.9)	−0.03
Statins use	5825 (4.1)	4973 (5.8)	−0.08	3564 (4.4)	4440 (5.5)	−0.05
Genetic susceptibility to malignant neoplasm	100 (0.1)	77 (0.1)	−0.01	63 (0.1)	72 (0.1)	−0.004
Overweight and obesity	103 913 (72.6)	69 765 (80.7)	−0.19	65 427 (80.9)	64 483 (79.7)	0.03
Other long-term (current) drug therapy	26 683 (18.7)	6851 (7.9)	0.30	7292 (9)	6842 (8.5)	0.02
Tobacco use	2787 (1.9)	902 (1)	0.07	854 (1.1)	893 (1.1)	−0.005
Essential (primary) hypertension	42 540 (29.7)	28 679 (33.2)	−0.07	25 071 (31)	25 485 (31.5)	−0.01
Disorders of lipoprotein metabolism and other lipidemias	33 724 (23.6)	25 278 (29.2)	−0.13	20 866 (25.8)	22 588 (27.9)	−0.05
Bariatric surgery status	7971 (5.6)	2022 (2.3)	0.16	1927 (2.4)	2021 (2.5)	−0.008
Depressive episode	14 591 (10.2)	8126 (9.4)	0.03	7767 (9.6)	7797 (9.6)	−0.001
Encounter for screening for malignant neoplasms	13 127 (9.2)	15 206 (17.6)	−0.26	9939 (12.3)	10 935 (13.5)	−0.04
Personal history of malignant neoplasm	2636 (1.8)	603 (0.7)	0.10	550 (0.7)	602 (0.7)	−0.008
Family history of primary malignant neoplasm	3965 (2.8)	1530 (1.8)	0.07	1336 (1.7)	1493 (1.8)	−0.02
Long-term (current) use of nonsteroidal anti-inflammatory drugs	1778 (1.2)	208 (0.2)	0.11	245 (0.3)	208 (0.3)	0.009
Alcohol use, unspecified	644 (0.5)	214 (0.2)	0.03	189 (0.2)	208 (0.3)	−0.005
Nicotine dependence	9236 (6.5)	2213 (2.6)	0.18	2066 (2.6)	2213 (2.7)	−0.011
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	2883 (2)	695 (0.8)	0.10	641 (0.8)	694 (0.9)	−0.007
Body mass index 30-39 kg/m^2	52 692 (36.8)	33 364 (38.6)	−0.04	32 449 (40.1)	31 594 (39.1)	0.022

Values are n (%) unless otherwise specified.
GLP-1, glucagon-like peptide-1; SD, standard deviation; SMD, standardized mean difference.

incidence functions were derived via Kaplan—Meier estimates. The data used in this study was collected in June 2025 from the TriNetX Research Network. Analyses were completed with the downloaded dataset on 25 August 2025. Statistical procedures including propensity score matching, Kaplan—Meier estimation, Cox proportional HR model, and analysis of IPTW were executed using R (version 4.5.1).

For the purpose of sensitivity analysis, exposure was redefined at the drug level, incorporating ingredient and brand information from RxDrug and National Drug Code identifiers. In addition, we calculated the E-value to quantify the potential influence of unmeasured confounding.[25] To evaluate the robustness of findings, we applied a Fine—Gray subdistribution hazards approach to address the competing risk of death.[26] To address the possibility of reverse causality, we carried out sensitivity analyses excluding patients who developed OACs within the first 6 months and, separately, within the first 12 months after treatment initiation.[27] To avoid calendar-time bias, we incorporated calendar year of cohort entry into the propensity score model and repeated the matching as a sensitivity analysis.[28]

RESULTS

The study population comprised 229 467 nondiabetic individuals diagnosed with obesity, defined as BMI $\geq$30 kg/m^2, with a mean age of 47.2 (SD 14.8). Of these, 71.8% (n =164 815) were female, and 28.2% (n = 64 652) were male. Among the cohort, 37.7% (n = 86 422) used GLP-1RAs, and 62.3% (n = 143 045) used diet or exercise. Among GLP-1RA users, 74.5% (n = 64 388) were women (Table 1). Median follow-up was 2 years (interquartile range 1-2) for patients using GLP-1RAs. After propensity weighting, all covariates were well balanced (standardized differences $<$10%) (Table 1).

Figure 1 shows comparison of the cumulative risk of 13 OACs in patients using GLP-1RAs and in those who received diet or exercise consultation without GLP-1RAs. Compared with diet or exercise consultation, GLP-1RA use was significantly associated with a reduced cumulative incidence of OACs (HR 0.59, 95% CI 0.53-0.67) in the propensity score matched analysis. Supplementary data, available at https://doi.org/10.1016/j.annonc.2026.04.013. Figure 2 shows the forest plot of the incidence of individual OACs.

Subgroup analyses

Stratified by gender. Among women, GLP-1RA use was associated with a reduction in overall cancer incidence (HR 0.65, 95% CI 0.57-0.74) (Figure 1). Similarly in men, GLP-1RA use was also associated with reduced overall cancer incidence (HR 0.32, 95% CI 0.23-0.44) (Figure 1). Results of site-specific analyses of women and men are shown in Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.annonc.2026.04.013.

Stratified by BMI. In analyses stratified by BMI, GLP-1RA use conferred similar associations across strata. Among patients with BMI 30-40 kg/m^2, GLP-1RA use was associated with significantly lower cumulative risks of cancers (HR 0.63, 95% CI 0.54-0.73). In the BMI $\geq$40 group, a statistically significant association with lower overall cancer incidence was observed (HR 0.57, 95% CI 0.46-0.69). Results of site-specific analyses of BMI 30-40 and BMI $\geq$40 groups are shown in Supplementary Figures S3 and S4, available at https://doi.org/10.1016/j.annonc.2026.04.013.

Stratified by race. Among the white population, use of GLP-1RAs was associated with a lower overall incidence of cancer (HR 0.54, 95% CI 0.47-0.62) (Figure 1). However, this association was not seen among black patients (HR, 0.77; 95% CI, 0.58 to 1.03) (Figure 1). Results of site-specific analyses of white and black race are shown in Supplementary Figure S5 and S6, available at https://doi.org/10.1016/j.annonc.2026.04.013.

Stratified by GLP-1RA formulation. Patients with exposure to semaglutide had a statistically significant reduction in cumulative cancer incidence (HR 0.80, 95% CI 0.68-0.94) (Figure 1). Patients with exposure to tirzepatide demonstrated similar findings, associated with decreased overall cancer incidence (HR 0.31; 95% CI 0.22-0.44) (Figure 1). The cumulative cancer incidence was lower among tirzepatide users compared with semaglutide users. No intergroup statistical testing was carried out because the analyses were designed to compare each GLP-1RA formulation separately with diet or exercise consultation rather than to conduct a head-to-head comparison between formulations. Results of site-specific analyses of semaglutide and tirzepatide individuals are shown in Supplementary Figures S7 and S8, available at https://doi.org/10.1016/j.annonc.2026.04.013.

IPTW analysis

IPTW analysis yielded results consistent with the propensity score matched analysis. Compared with diet or exercise consultation, treatment with GLP-1RAs was associated with a reduced risk of the composite outcome of OACs (HR 0.59, 95% CI 0.52-0.67) (Figure 1). Subgroup analyses demonstrated consistent direction of association. Results of site-specific analyses are shown in Supplementary Figures S9-S19, available at https://doi.org/10.1016/j.annonc.2026.04.013.

Sensitivity analyses

Results were consistent when accounting for dosage and formulation of the medications (Supplementary Figures S18 and S19). To evaluate the potential impact of unmeasured confounding on the association between GLP-1RA use and OACs, E-values for HRs were derived from the Cox proportional hazards models.[25] After adjustment for measured covariates, the E-value was 2.81, which indicates that an unmeasured confounder would need to be associated with both GLP-1RA use and OAC risk

Outcome	GLP-1RA, No (%)	Diet or exercise, No (%)	Hazard ratio (95% CI)
Propensity-Score-Matched Analysis			
Overall cancer	434 (0.54)	732 (0.90)	0.59 (0.53-0.67)
Male	48 (0.23)	151 (0.73)	0.32 (0.23-0.44)
Female	379 (0.64)	581 (0.97)	0.65 (0.57-0.74)
BMI < 40	274 (0.56)	437 (0.89)	0.63 (0.54-0.73)
BMI ≥ 40	152 (0.50)	268 (0.88)	0.57 (0.46-0.69)
White	312 (0.50)	575 (0.93)	0.54 (0.47-0.62)
Black	82 (0.66)	106 (0.85)	0.77 (0.58-1.03)
Semaglutide	253 (0.73)	316 (0.92)	0.80 (0.68-0.94)
Tirzepatide	41 (0.26)	131 (0.83)	0.31 (0.22-0.44)
Inverse Probability of Treatment Weighting Analysis			
Overall cancer	480 (0.56)	1334 (0.93)	0.59 (0.52-0.67)
Male	51 (0.23)	344 (0.81)	0.27 (0.19-0.38)
Female	429 (0.67)	990 (0.99)	0.67 (0.59-0.76)
BMI < 40	299 (0.56)	877 (0.97)	0.58 (0.50-0.69)
BMI ≥ 40	181 (0.54)	457 (0.87)	0.58 (0.48-0.70)
White	343 (0.52)	939 (0.97)	0.51 (0.44-0.59)
Black	86 (0.67)	216 (0.84)	0.72 (0.55-0.94)
Semaglutide	253 (0.73)	1334 (0.93)	0.75 (0.62-0.91)
Tirzepatide	41 (0.26)	1334 (0.93)	0.26 (0.17-0.39)

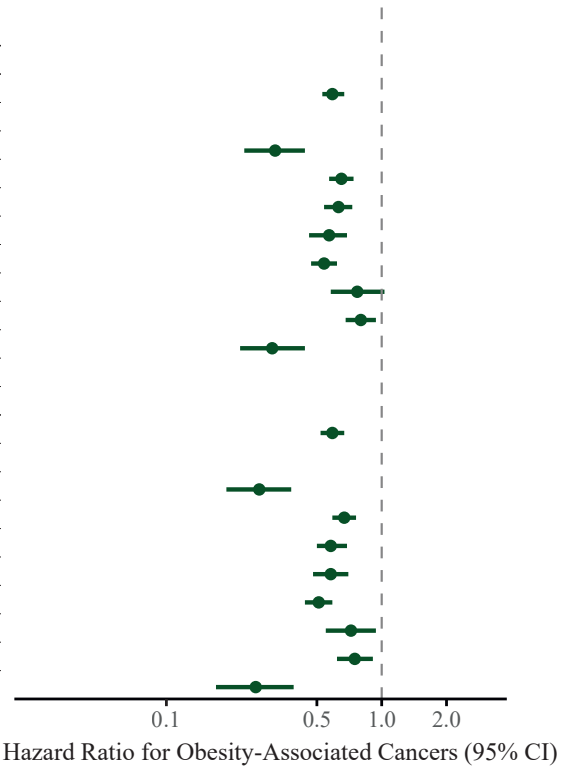

Figure 1. Associations between GLP-1RAs in obesity-associated cancers. Hazard ratios were calculated using Cox proportional hazards models. The GLP-1RAs were matched 1:1 to diet or exercise consultation using propensity score matching with a caliper of 0.1, and the balance was checked for all standardized mean differences <0.1. In addition, inverse probability of treatment weighting was conducted and showed consistent results. The horizontal bars represent the 95% CIs.
BMI, body mass index; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

by at least an HR of 2.81 to shift the estimate to the null. E-values for subgroups showed that an unmeasured confounder would need to have a corresponding HR as low as 2.47 or as high as 5.73 to have any effect on shifting the findings to the null (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2026.04.013). To

Outcome	GLP-1RA, No (%)	Diet or exercise, No (%)	Hazard ratio (95% CI)
Propensity-Score-Matched Analysis			
Multiple myeloma	17 (0.02)	46 (0.06)	0.37 (0.21-0.64)
Pancreatic cancer	14 (0.02)	35 (0.04)	0.40 (0.22-0.74)
Endometrial cancer	35 (0.04)	83 (0.10)	0.42 (0.28-0.63)
Colorectal cancer	45 (0.06)	91 (0.11)	0.49 (0.35-0.71)
Thyroid cancer	48 (0.06)	77 (0.10)	0.62 (0.43-0.89)
Kidney cancer	46 (0.06)	64 (0.08)	0.72 (0.49-1.05)
Ovarian cancer	17 (0.02)	23 (0.03)	0.74 (0.39-1.38)
Breast cancer	208 (0.26)	251 (0.31)	0.83 (0.69-0.996)

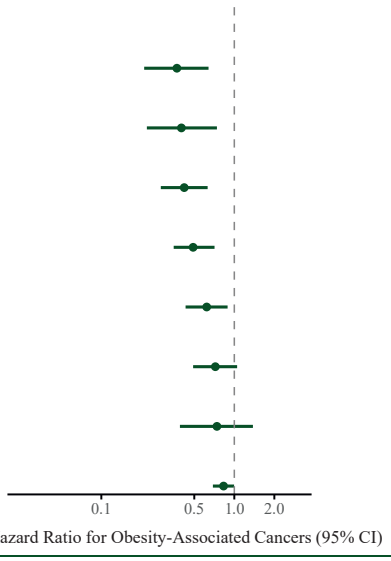

Figure 2. Subgroup analysis of site-specific obesity-associated cancers. Hazard ratios were calculated using Cox proportional hazards models. The GLP-1RAs were matched 1:1 to diet or exercise consultation using propensity score matching with a caliper of 0.1, and the balance was checked for all standardized mean differences of <0.1. In addition, inverse probability of treatment weighting was conducted and showed consistent results. The horizontal bars represent the 95% CIs. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

address competing events, we applied a Fine—Gray subdistribution hazards model treating death as a competing outcome (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2026.04.013). The results were consistent with the main analysis and supported the robustness of our findings under competing risk conditions. Sensitivity analyses excluding patients who developed OACs within the first 6 months and, separately, within the first 12 months after treatment initiation yielded results consistent with the primary analysis, suggesting that the observed association was unlikely to be driven by early events or reverse causation (Supplementary Figures S20-S23, available at https://doi.org/10.1016/j.annonc.2026.04.013). Calendar year of cohort entry was incorporated into the propensity score model, and matching was repeated as a sensitivity analysis showing consistent results. After matching, the distribution of calendar year was well balanced between the two groups (all standardized mean differences <0.1). A 2-year follow-up window was applied as described above, and follow-up duration was well balanced between groups (Supplementary Figures S24 and S25, available at https://doi.org/10.1016/j.annonc.2026.04.013).

DISCUSSION

In this large real-world cohort of obese, nondiabetic adults, use of GLP-1RAs for weight management was associated with a significantly lower cumulative incidence of OACs compared with diet or exercise consultation alone. Importantly, this association was consistent across subgroups, except for black race, and remained robust across analytic methods and sensitivity analyses.

Our study extends existing evidence by focusing specifically on obese, nondiabetic individuals using GLP-1RAs for weight management—a population that has expanded rapidly worldwide. Previous meta-analyses of GLP-1RA trials have demonstrated limited evidence of cancer protection, follow-up durations were short and trials were not designed to evaluate cancer outcomes.[29] Subsequent retrospective studies have reported reduced incidence of OACs among GLP-1RA users, primarily in populations with type 2 diabetes and obesity.[13,14] A key strength of this study is the use of a target trial emulation framework to evaluate the association between GLP-1RA use and cancer outcomes within a population-based observational dataset. By explicitly defining eligibility criteria, treatment strategies, time zero, follow-up, and analytic estimands to mirror a hypothetical randomized trial, this approach reduces common sources of bias inherent in conventional observational designs, including immortal time bias and inappropriate handling of treatment initiation.[15] These methodological considerations are particularly important when studying medications with rapidly increasing uptake and outcomes, such as cancer, that have long latency periods.

The age and sex distribution of our cohort differs meaningfully from prior studies examining GLP-1RA use and cancer risk. Randomized trials of GLP-1RAs for obesity management have enrolled younger participants and a higher proportion of women compared to diabetes management trials, a demographic profile closely aligned with our cohort.[6-11] Demonstrating an association between GLP-1RA use and reduced OAC incidence in this younger, nondiabetic population is particularly relevant given the rising burden of obesity-related malignancies diagnosed before midlife in high-income regions.

The association between GLP-1RA use and reduced OAC incidence was generally consistent across subgroups, although heterogeneity by sex and race was observed. The greater apparent benefit among men compared with women warrants further investigation. Although the underlying mechanisms remain uncertain, differential treatment persistence may contribute, as women report higher rates of gastrointestinal adverse events with GLP-1RAs, which may limit duration of exposure.[30,31] Notably, GLP-1RA use was not associated with a reduced cumulative incidence of OACs among black patients. This finding should be interpreted cautiously. Structural inequities in access to cancer screening and early detection, as well as differences in baseline cancer susceptibility, may attenuate observable associations in real-world data. Evidence shows black individuals experience higher risks for several OACs (e.g. colorectal, pancreatic), whereas risks for others are similar or lower compared with white populations, suggesting that biological, environmental, and health system factors may jointly influence observed outcomes.[32]

Although this study was not designed to detect site-specific effects for individual malignancies, the direction and magnitude of the associations across multiple cancer types were broadly consistent with prior reports (Figure 2). We observed a consistent reduction in endometrial cancer incidence among GLP-1RA users, aligning with established etiologic links between obesity and endometrial carcinogenesis.[33,34] In contrast, null associations for ovarian cancer and meningioma likely reflect the relatively young age of the cohort and limited follow-up for cancers with longer latency.[35,36] In addition, for meningioma, event counts were extremely low, which precluded estimation of HRs and meaningful inference. Consistent with prior studies, GLP-1RA use was not associated with a significant change in breast cancer incidence.[13,14]

Given the various new formulations of GLP-RAs being used for weight management, we examined whether there was a differential association of cancer risk with different formulations. Interestingly, the HRs tended to be lower with tirzepatide than with semaglutide. The biological basis for this apparent difference remains uncertain. One potential explanation is that tirzepatide is considered a dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide receptor coagonist, which may result in distinct efficacy.[3,4] However, the two groups were not statistically comparable, because each formulation was evaluated separately against diet or exercise consultation.

Limitations

Several limitations merit consideration. Although target trial emulation improves causal interpretability, the retrospective design precludes definitive causal inference, and residual confounding cannot be excluded despite the use of propensity score methods and inverse probability weighting, particularly because differences in the intensity and adherence to lifestyle interventions in the comparator groups could not be fully captured. Exposure misclassification is possible given prescription-based definitions and the emergence of compounded formulations, which would likely bias estimates toward the null.[37] Observed differences between formulations should be interpreted cautiously, as tirzepatide users were more likely to initiate therapy in later calendar years with shorter follow-up and potentially different baseline risk profiles. Follow-up duration was relatively short, reflecting the recent expansion of GLP-1RA use for obesity management, and may underestimate associations for cancers with longer latency. Finally, underlying biological mechanisms could not be directly evaluated.

Despite these limitations, the potential implications are substantial. OACs account for ∼40% of incident cancers in high-income countries, and their incidence is rising most rapidly among younger adults.[38,39] If confirmed in prospective studies, GLP-1RAs may be associated with a broader clinical profile that extends beyond obesity management to include potential effects on cancer risk. These findings underscore the need for long-term prospective trials and postmarketing surveillance frameworks that incorporate cancer outcomes, particularly in younger, obese populations with increasing oncologic risk.

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DISCLOSURE

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