GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity: A New Chapter in Metabolic Oncology?

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OBESITY

STRUCTURED ABSTRACT

Question: Is the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) associated with cancer incidence among adults who are overweight or obese?

Design: Target trial emulation using a retrospective new-user cohort design with 1:1 time-dependent propensity score matching.

Setting: OneFlorida+ network, consisting of 14 health systems, and ~20 million patients from 2014–2024.

Patients: Adults ≥18 years eligible for anti-obesity medication. Excluded patients <18 years with active malignancy or who were pregnant at baseline.

Exposure: GLP-1RA initiation (liraglutide, semaglutide, tirzepatide).

Outcomes: Incidence of 13 obesity-related cancers (bladder, colorectal, kidney, breast, endometrial, thyroid, pancreatic, meningioma, liver, upper gastrointestinal, ovarian, multiple myeloma, and prostate) and lung cancer.

Data Analysis: Matching with Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs; prespecified site-specific analyses, sensitivity checks, heterogeneity of treatment effect (HTE), and individualized treatment effect analyses using machine learning.

Results: In 86,632 matched adults (43,317 GLP-1RA initiators and 43,315 nonusers; mean age 52.4 years; 68.2% women; 50.7% with type 2 diabetes), overall cancer incidence was lower among GLP-1RA users compared with nonusers (13.6 vs 16.4 per 1,000 person-years), corresponding to an HR of 0.83 (95% CI, 0.76–0.91; $P = 0.02$) (**Figure 1**).[1] Site-specific analyses showed reduced risks for endometrial (HR 0.75; 95% CI, 0.57–0.99; $P = 0.05$), ovarian (HR 0.53; 95% CI, 0.29–0.96; $P = 0.04$), and meningioma (HR 0.69; 95% CI, 0.48–0.97; $P = 0.05$), with a possible increased risk of kidney cancer (HR 1.38; 95% CI, 0.99–1.93; $P = 0.04$).

Sensitivity analyses, including Fine-Gray competing risk models and a composite gynecologic cancer model, confirmed robustness of results (HR 0.69; 95% CI, 0.48–0.97 for combined endometrial/ovarian cancer). Heterogeneity analyses suggested the strongest benefit among younger women and those with metabolic risk, while the kidney cancer signal was more pronounced in patients <65 years and overweight (BMI 27–29.9).
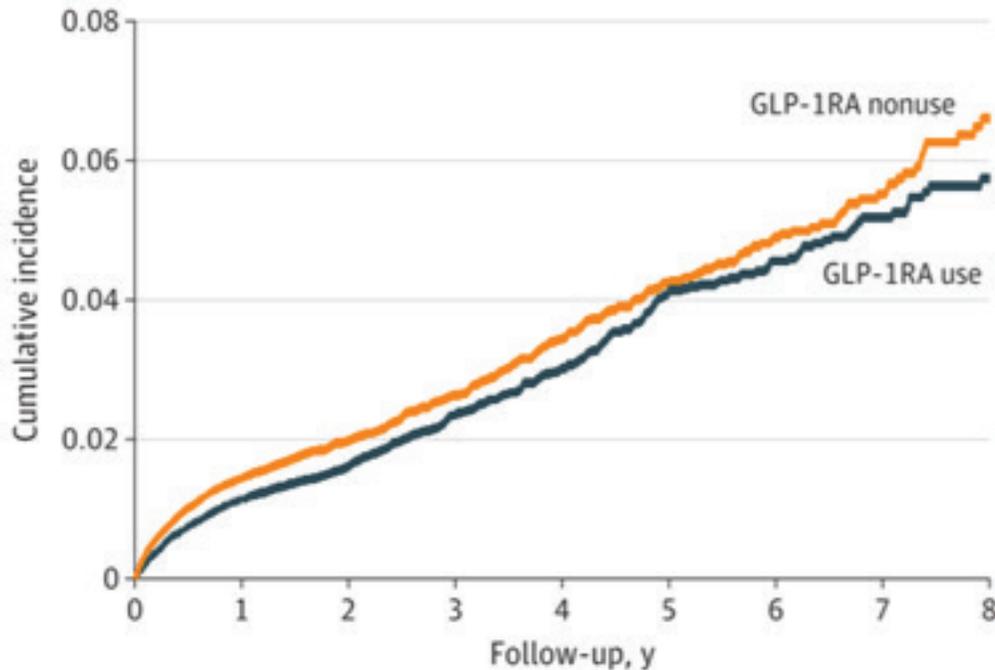
Figure 1. Cumulative incidence of overall cancer in patients receiving GLP-1RAs compared with patients not receiving GLP-1RAs. Kaplan-Meier curves demonstrating lower cumulative incidence of overall cancer among GLP-1RA initiators (blue line) compared with matched nonusers (orange line) during up to 8 years of follow-up.

COMMENTARY

Why Is This Important?

GLP-1RAs have transformed obesity and diabetes care, providing substantial cardiometabolic benefits.[2,3] However, safety concerns, particularly around cancer risk, have persisted since early rodent thyroid studies.[4] With over 137 million US adults now eligible for GLP-1RAs, even modest changes in cancer risk carry major public health implications.

Obesity is also a leading driver of gastrointestinal (GI) and hepatobiliary cancers, from colorectal cancer to hepatocellular carcinoma, making any therapy that modifies obesity-related cancer risk directly relevant to gastroenterology practice.[5]

This study offers contemporary evidence on GLP-1RA association with overall cancer risk in adults with obesity, particularly for hormonally driven malignancies, while raising questions about kidney cancer that warrant ongoing vigilance. This study provides the most rigorous, contemporary evidence on GLP-1RA association with overall cancer risk, particularly for hormonally driven malignancies, while raising questions about kidney cancer that warrant ongoing vigilance. Importantly, it highlights heterogeneity of treatment effects, identifying subgroups who may derive the greatest benefit—or, conversely, experience potential harm from GPL1-RA use.[1]

Among 43,317 GLP-1RA users and 43,315 matched nonusers, overall cancer incidence was 13.6 vs 16.4 per 1,000 person-years, translating to a 17% lower risk with GLP-1RAs (HR 0.83; 95% CI 0.76–0.91; $P=0.02$). Reduced risks were seen for endometrial (HR 0.75; 95% CI, 0.57-0.99; $P=0.05$), ovarian (HR 0.53; 0.29-0.96; $P=0.04$), and meningioma cancers (HR 0.69; 95% CI,0.48-0.97]; $P=0.05$), while a possible increased risk of kidney cancer was observed (HR 1.38; 95% CI 0.99–1.93; $P=0.04$). Results were consistent across sensitivity analyses.

Caution

Despite its strengths – including a large sample size and propensity matching – this is an observational study that is subject to confounders and bias. Cancer latency may exceed the study's follow-up period, limiting the ability to detect long-term effects. Some cancers (e.g., ovarian, pancreatic) had relatively few events, producing wide confidence intervals. The kidney cancer signal, while intriguing, requires replication and may represent chance, confounding, or true risk. Generalizability may be limited beyond the OneFlorida+ network. Ultimately, these findings are hypothesis-generating and should not yet alter cancer screening guidelines.

My Practice

In my practice, where I increasingly prescribe GLP-1RAs for obesity and MASLD, these findings are highly reassuring. These findings are also highly relevant considering the recent FDA approval of GLP-1RAs for MASH with F2-3 fibrosis.

I can now counsel patients that GLP-1RAs not only promote weight loss and cardiometabolic benefits but may also reduce overall cancer risk, particularly for endometrial and ovarian cancers; two malignancies strongly linked to obesity and hyperinsulinemia. At the same time, I acknowledge the possible kidney cancer signal, which I discuss with patients as an area of active investigation rather than a reason to withhold therapy. I continue to emphasize adherence to lifestyle interventions and standard cancer screening, while framing GLP-1RAs as part of a comprehensive prevention strategy.

For Future Research

Longer-term studies are needed to capture cancers with long latency and validate site-specific signals. Mechanistic studies should clarify whether benefits arise from weight loss alone or direct GLP-1 receptor effects on tumor biology. Finally, focused work on GI and hepatobiliary cancers (where obesity and metabolic dysfunction are critical drivers) will be essential to fully define the oncologic

role of GLP-1RAs.

Conflict of Interest

The authors of this summary have no conflicts of interest to disclose.

Abbreviations

BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; HTE, heterogeneity of treatment effect; NIH, National Institute of Health.

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