THYROID
Volume 00, Number 00, 2025

DOI: 10.1089/thy.2024.0690

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Thyroid Cancer Risk with GLP-1 Receptor Agonists: Evidence, Knowledge Gaps, and the Path Forward

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Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA) have transformed the management of type 2 diabetes and obesity, demonstrating renal and neurocardiovascular benefits, as well as improvements in hepatic steatosis, in both individuals with and without type 2 diabetes.[1–3] Consequently, approximately 64 million prescriptions for GLP-1RA were dispensed in the United States between 2000 and 2015.[4] Furthermore, the initiation of GLP-1RA among patients without diabetes but with overweight or obesity increased by over 700% between 2019 and 2023.[5] Given their expanding use and the frequent need for long-term therapy, ensuring the safety of these medications is essential.

Preclinical studies demonstrated a link between GLP-1 RA exposure and medullary thyroid cancer in rodents.[6] In addition, GLP-1 receptors are more prominently expressed in human papillary thyroid cancer cells than in normal thyroid cells.[7] Based on the rodent data, the U.S. Food and Drug Administration has issued a boxed warning against the use of GLP-1RA by those with a personal or family history of medullary thyroid cancer and hereditary conditions associated with this type of cancer.[8] However, evidence regarding the risk of thyroid cancer in humans associated with GLP-1RA use remains conflicting. Secondary analyses from randomized controlled trials, observational studies, and meta-analyses have reported varying findings, with some suggesting an increased risk of thyroid cancer,[9,10] and others indicating no significant association following GLP-1RA initiation.[11–14]

In this issue of *Thyroid*, Baxter et al. present findings from their multisite cohort study and meta-analysis, which analyzed six population cohorts from Canada, Denmark, Norway, South Korea, Sweden, and Taiwan, spanning various time frames between 2009 and 2023.[15] The study aims to further clarify the risk of thyroid cancer in patients with type 2 diabetes treated with GLP-1RA. Patients included in the study were 40 years or older, had been treated with metformin in the prior year, and were initiating either GLP-1RA (98,147 participants; median follow-up of 1.8–3 years) or dipeptidyl peptidase-4 inhibitors (DPP-4i; 2,488,303 participants; median follow-up of 2.8–6.8 years). In an intention-to-treat analysis, the use of GLP-1RA was not associated with an increased risk of thyroid cancer compared with DPP-4i (adjusted HR: 0.81 [CI: 0.59–1.12]), and no trend was observed with increasing cumulative doses of GLP-1RA. When the comparison group shifted from DPP-4i to sulfonylureas, GLP-1RA use was linked to a higher risk of thyroid cancer (HR: 1.8 [CI: 1.2–2.5]). Supplementary analyses, including effect modification by age, GLP-1RA type, and sensitivity analyses (e.g., excluding baseline thyroid disorders or including *in situ* cancers), supported the primary findings. However, low event rates precluded stratification for medullary thyroid cancer risk.

The study by Baxter et al. stands out for its large scale and robust methodology. The inclusion of six population-based cohorts from diverse geographical settings enhances the generalizability of the findings. By employing a new-user active comparator design, the study effectively minimizes biases related to preexisting conditions or prior medication use. In addition, the rigorous adjustment for confounders through time-specific propensity scores and weighting further bolsters the validity of the results. Despite these strengths, several limitations warrant consideration. The median follow-up period of 1.8–3.0 years is insufficient to evaluate long-term risks, which is particularly relevant given the latency associated with thyroid cancer development after exposures such as radiation ($\sim$2.5 years).[16] Low event rates constrained subgroup analyses, particularly for medullary thyroid cancer, a subtype of specific interest due to its potential association with GLP-1RA in preclinical studies. Furthermore, although the overall sample size is large, the study's focus on populations with type 2 diabetes may limit its applicability

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to nondiabetic populations, a growing group of GLP-1RA users, particularly for obesity management.

In conclusion, despite these limitations, Baxter et al. using an intention-to-treat analysis (analysis of patients based on initial assignment rather than treatment received) and leveraging observational data (to include a larger, more representative sample) present findings consistent with randomized clinical trials comparing GLP1-RA to other medications, emphasizing that thyroid cancer incidence following GLP-1RA initiation is rare (absolute risk). These results contribute to the growing body of evidence suggesting that the benefits of GLP-1RA likely outweigh any potential thyroid-related risks, reinforcing confidence in the absence of a clinically significant short-term causal relationship between GLP-1RA and thyroid cancer. This provides reassurance to clinicians and patients, especially those without risk factors for medullary thyroid cancer.

However, further research is needed to address key questions regarding the potential association between GLP-1RA and thyroid cancer. If no causal relationship exists, why do some observational studies, particularly those using as-treated analyses (evaluating patients based on the treatment received), suggest an increased risk? This discrepancy may be explained by unmeasured confounders, such as weight and body mass index—factors associated with thyroid cancer that are notoriously challenging to capture accurately in large observational studies. These confounders might also explain this study subgroup analysis showing a higher risk of thyroid cancer with GLP-1RA only when compared with sulfonylureas, which might be less prescribed for obese patients due to concerns about weight gain.

Alternatively, the observed association could reflect differences in care pathways rather than a direct effect of GLP-1RAs. For example, heightened medical surveillance among GLP-1RA users—driven by concerns about thyroid cancer—may lead to increased use of thyroid ultrasound, a practice strongly associated with overdiagnosis of thyroid cancer. This hypothesis warrants further exploration, particularly as the widespread adoption of GLP-1RA is expected to grow. This growth could exacerbate the already significant use and overuse of thyroid ultrasound, leading to a surge in the detection of thyroid nodules and cancers, potentially resulting in increased rates of overtreatment.

In addition, further evaluations are needed to assess risk variations across diverse populations, such as younger individuals, those with obesity, nondiabetics, and patients with a prior history of thyroid cancer, as well as different thyroid cancer histology. These studies should aim to clarify the true magnitude—or absence—of risk for incident thyroid cancer and subtypes while also distinguishing between biological mechanisms and health care system-related factors driving the observed trends. By addressing these gaps, future research can provide a more nuanced understanding of the safety profile of GLP1-RA and further inform clinical decision-making.

Authors' Contributions

D.T.-T., N.M.S.O., and J.P.B. contributed to the conceptualization, literature review, and article preparation.

Author Disclosure Statement

D.T.-T. is a consultant for Immunovant but reports no conflicts of interest related to this publication. N.M.S.O. and J.P.B. have no relevant disclosures.

Funding Information

N.M.S.O. and J.P.B. were supported by the National Cancer Institute of the National Institutes of Health under Award Numbers K08CA248972 and R37CA272473, respectively. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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