Putting GLP-1 RAs and Thyroid Cancer in Context: Additional Evidence and Remaining Doubts

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Diabetes Care 2023;46:249–251 | https://doi.org/10.2337/dci22-0052

In this issue of *Diabetes Care*, Bezin et al. (1) report the findings of a population-based case-control study from France on the potential effects of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) on the incidence of thyroid cancer. The article is well written, the data are fit for purpose to study the short-term effects of antidiabetes drugs on cancer incidence, the observed moderate increase in relative risk seems plausible, and the conclusions are mostly supported by the data presented. In this commentary, we discuss three issues: misuse of *P* values, limitations of case-control designs in this setting, and overdiagnosis of thyroid cancer. We hope that these will help the reader put the study by Bezin et al. into context.

The authors single out GLP-1 RA use of 1–3 years as a concern. This selective reporting is inconsistent with their results and seems to be based solely on *P* value criterion. Estimates for duration of use $\leq$1 year and $>$3 years are very similar in magnitude, but their estimates are less precise and thus not statistically significant. Only highlighting statistically significant results and, conversely, ignoring any non–statistically significant results is a common mistake in medical research (2,3) and is also reflected in the authors' interpretation of their results in light of the literature. In fact, the results presented by Bezin et al. are very consistent with the previous literature, from randomized controlled trials (LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results] hazard ratio 1.66 [95% CI 0.40–6.95] [4]), a meta-analysis of 12 randomized controlled trials (odds ratio 1.54 [95% CI 0.4–6.0]) (5), and the previous nonexperimental studies (Dore et al., relative risk 1.4 [95% CI 0.4–2.4] [6], and Liang et al., odds ratio 1.46 [95% CI 0.98–2.19] [7]).

Bezin et al. used a case-control design nested in an underlying population-based cohort. The data source allows the enumeration of the underlying cohort, unbiased risk-set sampling, and estimation of the incidence rate or hazard ratio (as pointed out by the authors). In this setting where no additional data were collected, the case-control design offers no efficiency gain over the cohort study, and it has several drawbacks (8). First, the case-control design provides relative measures of effect only. When making treatment decisions, clinicians need to weigh potential benefit and harm. For outcomes that have vastly different incidences (e.g., cardiovascular disease versus thyroid cancer), this can only be done on the absolute, or risk difference, scale. A protective relative risk of 0.9 for a high incidence outcome (e.g., cardiovascular disease) can largely outweigh a relative risk of 2 for a very low-incidence adverse outcome (e.g., thyroid cancer). Only the comparison of absolute risk (including a severity weighting) allows clinicians and patients to assess benefit-harm balance.

Bezin et al. defined entry into the underlying cohort as "the date of first second-line antidiabetes drugs dispensing." Assuming that there is little entry and exit from the nationwide French health care insurance system, this definition would mostly capture initiation of GLP-1 RAs versus dipeptidyl peptidase 4 inhibitors or other second-line antidiabetes drug classes. Active comparators (ideally specific ones) and new users are an important study design tools to limit the potential for confounding by indication and other biases (9–11). Note that in settings with considerable late entry (e.g., U.S. claims data), such a definition would need to be combined with a washout period without prescriptions for the drug classes of interest to identify new users.

Globally, thyroid cancer is ranked 9th for incidence but not in the top 20 for mortality burden (12). Incidence is five times higher in developed compared with developing countries, with much of this disparity attributable to the use of imaging and diagnostic procedures in high-quality health care settings. Indeed, global incidence of thyroid cancer has increased rapidly in the past 30 years due to a 240% increase in small papillary tumors (13). Despite these rises, the mortality rate has remained low and stable—a hallmark characteristic of overscreening and overdiagnosis (12,14).

Overdiagnosis of well-differentiated papillary-cell malignancies, which are often subclinical when diagnosed via imaging as

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See accompanying article, p. 384.

well as slow growing and/or indolent, may be of increased concern in patients with diabetes due to overuse of low-value thyroid care in older and multimorbid adult patients (15–17). Indeed, in 2017, the United States Preventative Services Task Force issued a recommendation against screening for thyroid cancer in asymptomatic adults, giving the practice their lowest evidence rating of a D (indicating that the harms may outweigh the benefits), and more conservative staging and treatment guidelines have been recently established (18,19). Despite this, thyroid cancer overdiagnosis remains a persistent problem, with evidence that the majority of clinicians recommend tests that lead to overdiagnosis (20).

Established risk factors for thyroid cancer include goiter, nodules, family history, previous radiation exposure, obesity, and genetic syndromes (21). While some of these factors can be accounted for using claims data, the current study was unable to adjust for family history and obesity. Diabetes has also been shown to be associated with a 20–30% increased risk of thyroid cancer in several meta-analyses (22–24). This association may be attributable to chronic elevated levels of insulin or thyroid stimulating hormone, both of which are more likely in individuals with diabetes; the latter is also known to be related to increased use of asymptomatic thyroid screening. It is unclear whether exposure to GLP-1 RAs is associated with increased monitoring of thyroid stimulating hormone, neck imaging for reflux, or weight loss making nodules more evident, but if so, this could be indicative of a detection bias caused by increased outcome ascertainment among those treated with GLP-1 RAs (25). While the authors attempted to address the potential for detection bias by repeating their analysis with cases defined as receipt of thyroidectomy without a cancer diagnosis, thyroidectomy is only one of several common treatments for nonmalignant thyroid conditions (26).

While overdiagnosis is a concern for most thyroid cancers, the authors also report elevated GLP-1 RA–associated risk of the more aggressive types of thyroid cancer—medullary tumors, which arise from parafollicular cells. These tumors are faster growing and more likely to metastasize and may pose a greater risk of harm in older adults, but they comprise $<$5% of the global thyroid cancer burden (12). It is perhaps alarming that medullary tumors accounted for $>$15% of all thyroid cancer cases in this study's population of people with diabetes, which is a higher percentage of all thyroid tumors than typically observed in general populations. However, the validity of the authors' claims-based tumor type classification schema is unclear, and an important, and acknowledged, limitation. It is also potentially concerning that the current study observed increased risk with a minimum of 6 months latency period, which could point to a very short incubation period for GLP-1 RA–induced thyroid cancers or be a sign of a detection bias. Future research should prioritize linkage to tumor registry data, to better understand the potential impact on rare and aggressive thyroid cancer subtypes and vary the exposure lag to better characterize the incubation period.

In conclusion, given the prior evidence and the results reported by Bezin et al. in this issue of *Diabetes Care*, it is possible that GLP-1 RAs cause a moderate relative increase in thyroid cancer, but detection bias cannot be ruled out as an alternative explanation. Thyroid cancer is a rare outcome, however, and the potential increase in absolute risk is very small. Clinicians and patients need to always balance benefit and harm of treatments in light of their alternatives. In a population without specific risk factors for thyroid cancer, the benefits of GLP-1 RAs will largely outweigh the harm.

Funding and Duality of Interest. C.T. receives investigator-initiated research funding and salary support as principal investigator from the National Cancer Institute (R01-CA-264176), the Centers for Disease Control and Prevention (6-U48-DP006400–04–01), the Gordon and Betty Moore Foundation (GBMF11505), and as co-investigator from the National Cancer Institute (U01-CA-199277, R01-CA-225478). T.S. receives investigator-initiated research funding and support as principal investigator from the National Institute on Aging (R01AG056479) and as co-investigator from the National Institutes of Health (R01CA174453, R01HL118255, R01MD011680). He also receives salary support as Director of Comparative Effectiveness Research, North Carolina Translational and Clinical Sciences Institute, University of North Carolina, the Clinical and Translational Science Award (UL1TR002489), the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim), from pharmaceutical companies (Novo Nordisk), and from a generous contribution from Dr. Nancy A. Dreyer to the Department of Epidemiology, University of North Carolina at Chapel Hill. T.S. does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

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