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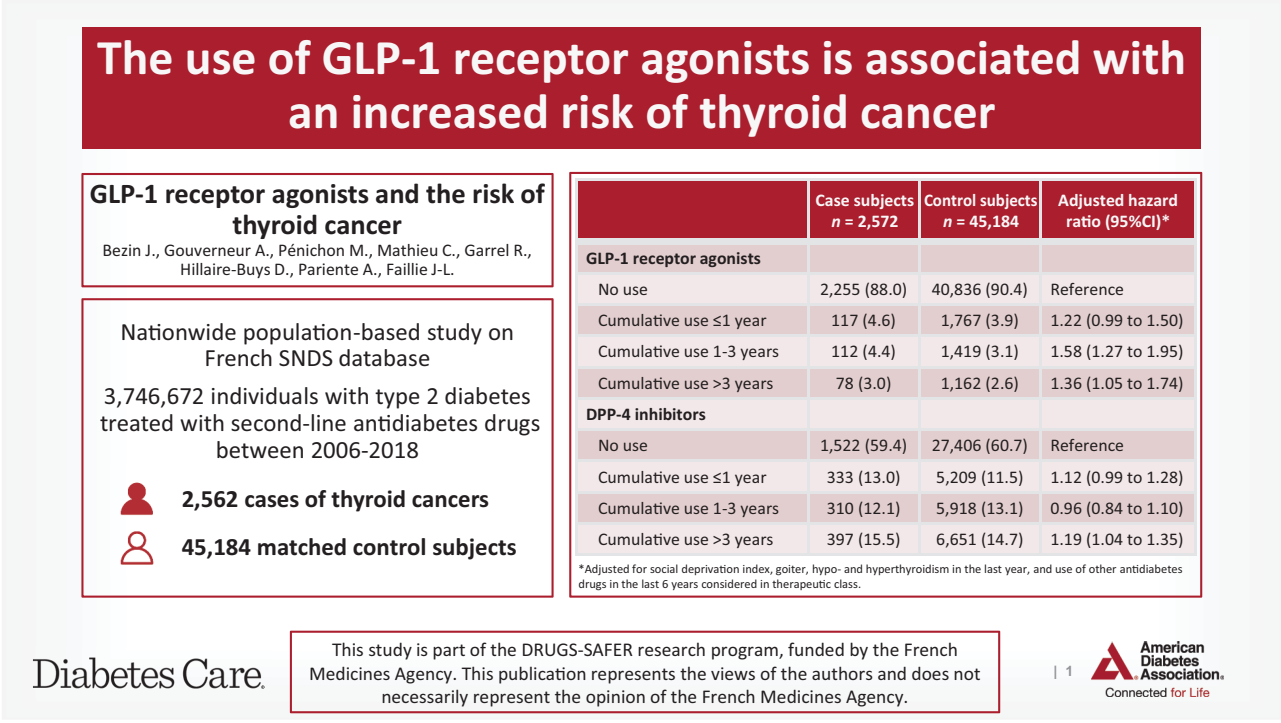

ARTICLE HIGHLIGHTS

- Preclinical studies suggest that GLP-1 RA have specific effects on the thyroid gland, potentially involving the development of thyroid cancer.
- Studies on this subject produced conflicting results, potentially due to a lack of statistical power.
- The results of this nationwide population-based study suggest that use of GLP-1 RA is associated with increased risk of thyroid cancer.
- The increased risk was higher in the case of 1–3 years of GLP-1 RA use.
- Clinicians should be aware of this potential risk in initiating a GLP-1 RA and carefully monitor exposed patients.

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer

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OBJECTIVE

To determine whether use of glucagon-like peptide 1 (GLP-1) receptor agonists (RA) is associated with increased risk of thyroid cancer.

RESEARCH DESIGN AND METHODS

A nested case-control analysis was performed with use of the French national health care insurance system (SNDS) database. Individuals with type 2 diabetes treated with second-line antidiabetes drugs between 2006 and 2018 were included in the cohort. All thyroid cancers were identified through hospital discharge diagnoses and medical procedures between 2014 and 2018. Exposure to GLP-1 RA was measured within the 6 years preceding a 6-month lag-time period and considered as current use and cumulative duration of use based on defined daily dose (≤1, 1 to 3, >3 years). Case subjects were matched with up to 20 control subjects on age, sex, and length of diabetes with the risk-set sampling procedure. Risk of thyroid cancer related to use of GLP-1 RA was estimated with a conditional logistic regression with adjustment for goiter, hypothyroidism, hyperthyroidism, other antidiabetes drugs, and social deprivation index.

RESULTS

A total of 2,562 case subjects with thyroid cancers were included in the study and matched with 45,184 control subjects. Use of GLP-1 RA for 1–3 years was associated with increased risk of all thyroid cancer (adjusted hazard ratio [HR] 1.58, 95% CI 1.27–1.95) and medullary thyroid cancer (adjusted HR 1.78, 95% CI 1.04–3.05).

CONCLUSIONS

In the current study we found increased risk of all thyroid cancer and medullary thyroid cancer with use of GLP-1 RA, in particular after 1–3 years of treatment.

Glucagon-like peptide 1 (GLP-1) receptor agonists (RA), such as exenatide, liraglutide, dulaglutide, and semaglutide, are second- or higher-line drugs commonly used in the treatment of type 2 diabetes. They induce direct activation of the GLP-1 receptor, which stimulates pancreatic insulin secretion in a glucose-dependent manner, while also inhibiting glucagon secretion (1).

Preclinical studies suggest that GLP-1 RA have specific effects on the thyroid gland, potentially involving the development of thyroid cancer, particularly of medullary thyroid cancer (C-cell carcinoma). Indeed, GLP-1 receptors are expressed in thyroid tissues, and carcinogenicity studies in rats and mice demonstrated a dose- and time-dependent increased risk of medullary carcinomas with GLP-1 RA (2–6). Based on these findings, the U.S. Food and Drug Administration (but not the European Medicines Agency) contraindicated the use of liraglutide, dulaglutide, exenatide extended release, and semaglutide in patients with a personal or family history of

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medullary thyroid cancer and multiple endocrine neoplasia type 2. Still, the relevance of animal carcinogenicity to humans has not been clearly determined for GLP-1 RA. An increased number of thyroid cancers was reported in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial evaluating liraglutide versus placebo, but the risk did not reach statistical significance (hazard ratio [HR] 1.66, 95% CI 0.40–6.95), as well as in a meta-analysis of 12 other clinical trials with liraglutide (odds ratio [OR] 1.54, 95% CI 0.40–6.02) (7,8). Nonetheless, these trials were not designed to assess thyroid cancer risk, and a lack of statistical power is suspected. In 2012 and 2018, two observational studies failed to show increased risk of thyroid cancer with exenatide (9,10). However, in the most recent, with use of two U.S. administrative databases, investigators found a nonsignificant trend toward increased risk of thyroid cancer with exenatide (OR 1.46, 95% CI 0.98–2.19) (10).

Consequently, there is currently uncertainty about the potential thyroid cancer risk associated with GLP-1 RA. Hence, the aim of the current study was to evaluate risk of thyroid cancer associated with use of GLP-1 RA in a nationwide real-world setting.

RESEARCH DESIGN AND METHODS

Data Source

This study was conducted with use of the nationwide French health care insurance system SNDS (Système National des Données de Santé) database, which represents 98.8% of the French population (>66 million people), from birth (or immigration) to death (or emigration). It includes anonymized individual-level data including sociodemographic data, outpatient drug dispensings and health care reimbursements, hospital discharge summaries, and registration status for a list of 30 costly and severe long-term diseases (LTD) eligible for full reimbursement of health care costs (e.g., diabetes, cancer). Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification, diagnoses related to hospitalizations or LTD according to ICD-10, and surgical and medical procedures according to the French classification (CCAM) (11). Neither ethics committee approval nor informed consent was required for this observational study based on French medico-administrative databases because of the anonymous nature of the data, by agreement of the French Data Protection Supervisor Authority (Comission Nationale de l'Informatique et des Libertés).

Study Cohort

We identified a base cohort of patients with type 2 diabetes treated with second-line antidiabetes drugs (GLP-1 RA, dipeptidyl peptidase 4 [DPP-4] inhibitors, or a multitherapy combining metformin, sulfonylureas, repaglinide, α-glucosidase inhibitors, or thiazolidinediones, excluding insulin monotherapy or combination of insulins [see Supplementary Table 1]) with at least three dispensings or two dispensings with at least one large package within a 1-year period between 1 January 2006 and 31 December 2018. Sodium–glucose cotransporter-2 inhibitors were not marketed in France during the study period. Cohort entry was defined as the date of first second-line antidiabetes drugs dispensing. We excluded the patients not covered by the general scheme; this scheme represents nearly 80% of the entire French population.

Case and Control Subject Definition

All incident cases of thyroid cancer between 1 January 2014 and 31 December 2018 were identified with ICD-10 codes for thyroid cancer in hospital discharge primary diagnoses, in LTD, or in hospital discharge–associated diagnoses with at least one medical procedure associated with thyroid cancer (Supplementary Table 2). The date of the first thyroid cancer record was considered as the index date. We excluded patients with <8 years of history before the index date, with history of cancer, with history of radiotherapy, and with pregnancy in the last year. Each case subject was matched to a maximum of 20 control subjects by age (in years), sex, and duration of diabetes (in 2-year class between 0 and 8 years, and then ≥8 years) with the risk-set sampling procedure. For each control subject, the date of thyroid cancer of the matched case subject was considered as the index date, and the same exclusion criteria as for the case subjects were applied to control subjects. Medullary thyroid cancers were identified from among these selected case subjects on the basis of the presence of serum calcitonin test/carcinoembryonic antigen (CEA) test or a treatment with vandetanib (Supplementary Table 2).

Exposure Definition

We introduced a lag-time period by shifting the index date 6 months earlier for both case and control subjects to reduce the risk of protopathic bias and to ensure that exposure to antidiabetes drugs indeed preceded the onset of cancer. For each patient, we identified all dispensings of GLP-1 RA as well as DPP-4 inhibitors (another class of incretin-based antidiabetes drugs) in the 6 years preceding the lag time period. For each dispensing, we estimated the duration of treatment from packaging size and treatment unit dosage and using the treatment daily dose defined for the drug (12). Thereafter, according to these treatment episodes, exposure was considered according to two definitions: *1*) history of use, nonuser (reference group), current user (ongoing treatment at the beginning of the lag time period), and past user (treatment in the 6 years preceding the lag time period but stopped before the start of the lag time period), and *2*) cumulative duration of use, nonuser (reference group), ≤1 year, 1–3 years, and >3 years.

Statistical Analysis and Sensitivity Analyses

Descriptive analyses were performed to compare characteristics between case and control subjects at the beginning of the lag time period. Data for qualitative variables are presented as number and proportion of patients in each group and continuous variables as median and interquartile range (IQR). Given that we included all available cases in the database and that the study sample size was determined by the disease incidence, we did not perform a formal power calculation.

A conditional logistic regression model was used to compute the ORs with 95% CIs. When ORs derived from a conditional logistic regression model are estimated in a nested case-control study where control subjects are selected with the risk-set sampling procedure, they can be related to HRs derived from a Cox regression model in which the exposure of interest is modeled as a time-dependent variable (13,14). Thus, the estimated risks were presented as HRs with their 95% CIs. Adjusted HRs

were estimated through adding potential confounding factors at the lag time period in the model, including social deprivation index, goiter, hypothyroidism and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered by therapeutic class (Supplementary Tables 1 and 3).

Secondary and sensitivity analyses were performed to assess the validity and robustness of the initial study results. Secondary analyses included *1*) stratification according to sex and *2*) use of thyroidectomy without cancer as a definition for cases (identification method in Supplementary Table 2) to study the effect of thyroidectomy. Sensitivity analyses were performed with changes of lag time period: 3 months and 12 months.

Complementary Pharmacovigilance Analyses

To further assess these potential risks, we performed an analysis of the World Health Organization's pharmacovigilance database VigiBase. VigiBase includes >23 million individual case safety reports from >150 countries worldwide. Using VigiBase data from 28 April 2005 (first market authorization for a GLP-1 RA) to 1 March 2021, we conducted disproportionality analyses to estimate the association between GLP-1 RA use and the risk of differential reporting of thyroid cancer, compared with all other antidiabetes drugs excluding insulins (15). Nonserious cases were excluded. Associations were estimated with use of two disproportionality measures: proportional reporting ratio (PRR) and Bayesian information component (IC). A signal of disproportionate reporting was considered if the 95% CI lower limit of PRR exceeded 1 or if the 95% credibility interval (0.025) lower limit of IC exceeded 0. Drugs were identified with ATC codes and cases of thyroid cancer with Medical Dictionary for Regulatory Activities (MedDRA) classification (Supplementary Table 4). No ethics review nor informed consent was required for using this existing and anonymized database.

All analyses were performed with SAS statistical software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Between 1 January 2006 and 31 December 2018, a total of 3,746,672 patients with type 2 diabetes were identified from the French SNDS nationwide database. Among them, 4,466 had an incident thyroid cancer between 1 January 2014 and 31 December 2018, and 1,900 were then excluded, mainly for a history of cancer (69.2%) and insufficient history in the database (30.6%). Four could not be matched to at least one control subject and were excluded (Fig. 1). We included 2,562 case and 45,184 matched control subjects. Median age at the index date was 64 years (IQR 56–71 for case and 57–71 for control subjects), and nearly two-thirds were female (67.0% and 67.2%, respectively). At baseline, case subjects were more likely than control subjects to have goiter (3.7% vs. 0.3%), hypothyroidism (23.9% vs. 13.1%), hyperthyroidism (5.6% vs. 0.5%), hypertension (75.2% vs. 68.9%), or treatment by nonsteroidal anti-inflammatory drugs (44.3% vs. 39.7%) (Table 1). Before the lag time period, 307 (12.0%) case and 4,348 (9.6%) control subjects had ever been exposed to GLP-1 RA. Of those, 253 (82.4%) case and 3,524 (81.0%) control subjects had been exposed to liraglutide and 82 (26.7%) case and 1,125 (25.9%) control subjects to exenatide.

The adjusted analysis showed that increased risk of all thyroid cancer was associated with current use of GLP-1 RA (HR 1.46, 95% CI 1.23–1.74) and cumulative use from 1 to 3 years (HR 1.58, 95% CI 1.27–1.95) and over 3 years (HR 1.36, 95% CI 1.05–1.74). Analysis on medullary thyroid cancer type showed a higher risk associated with GLP-1 RA (HR 1.78, 95% CI 1.04–3.05 for 1–3 years of GLP-1 RA use).

The association for current use of DPP-4 inhibitors was close to significance but weak (HR 1.10, 95% CI 0.99–1.22) and significant but weak for cumulative use over 3 years (HR 1.19, 95% CI 1.04–1.35) (Table 2).

With stratification by sex, the analyses yielded similar results, with a higher risk for cumulative use from 1 to 3 years of GLP-1 RA in men (HR 2.10, 95% CI 1.44–3.06) and women (HR 1.40, 95% CI 1.08–1.81). However, the risk for cumulative use over 3 years of GLP-1 RA was only higher for women (HR 1.44, 95% CI 1.08–1.92, for women and HR 1.08, 95% CI 0.62–1.88, for men). Use of DPP-4 inhibitors was only associated with a higher risk of thyroid cancer for women exposed for >3 years (HR 1.34, 95% CI 1.15–1.57) (Supplementary Table 5 and Supplementary Table 6). Secondary analysis performed with thyroidectomy without cancer included for cases showed no increased risk associated with GLP-1 RA or DPP-4 inhibitors (Supplementary Table 7). The sensitivity analyses with modified lag time period duration led to consistent results (Supplementary Tables 8 and 9).

Complementary pharmacovigilance analyses identified 606 spontaneous reports of thyroid cancers with GLP-1 RA, the main suspects being exenatide (*n* = 374 [61.7%]) and liraglutide (*n* = 206 [34.0%]). Disproportionality analyses showed signals of disproportionate reporting with GLP-1 RA for thyroid cancer (PRR 30.5,

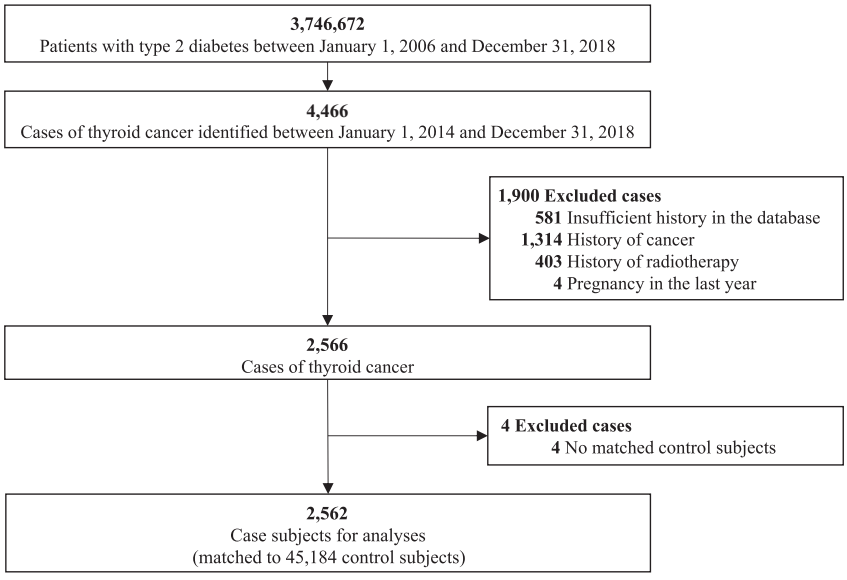

Figure 1—Flowchart of included case and control subjects.

Table 1—Baseline characteristics of case and control subjects at the beginning of the lag time period

	Case subjects, *n* = 2,562	Control subjects, *n* = 45,184
Age, years, median (IQR)	64 (56–71)	64 (57–71)
Sex		
Male	845 (33.0)	14,813 (32.8)
Female	1,717 (67.0)	30,371 (67.2)
Duration of diabetes (years)		
0–1	296 (11.5)	4,345 (9.6)
2–3	316 (12.3)	4,744 (10.5)
4–5	352 (13.7)	5,565 (12.3)
6–7	313 (12.2)	5,275 (11.7)
≥8	1,285 (50.2)	25,255 (55.9)
Antidiabetes drugs		
GLP-1 RA	307 (12.0)	4,348 (9.6)
DPP-4 inhibitors	1,040 (40.6)	17,778 (39.3)
Insulins	494 (19.3)	9,124 (20.2)
Metformin	2,037 (79.5)	35,700 (79.0)
Sulfonylureas	1,118 (43.6)	20,462 (45.3)
Repaglinide	387 (15.1)	6,182 (13.7)
α-Glucosidase inhibitors	193 (7.5)	3,683 (8.2)
Thiazolidinediones	159 (6.2)	3,582 (7.9)
Comorbidities		
Goiter	95 (3.7)	125 (0.3)
Hypothyroidism	613 (23.9)	5,933 (13.1)
Hyperthyroidism	144 (5.6)	220 (0.5)
Coronary heart disease	206 (8.0)	3,667 (8.1)
Stroke	63 (2.5)	1,085 (2.4)
Hypertension	1,926 (75.2)	31,144 (68.9)
Peripheral artery occlusive disease	71 (2.8)	1,299 (2.9)
Chronic kidney disease	58 (2.3)	893 (2.0)
Obesity	302 (11.8)	3,812 (8.4)
Smoker	622 (24.3)	9,336 (20.7)
Concomitant drugs		
β-Blocking agents	508 (19.8)	8,023 (17.8)
Diuretics	862 (33.7)	13,636 (30.2)
Calcium channel blockers	602 (23.5)	9,436 (20.9)
ACE inhibitors	720 (28.1)	11,516 (25.5)
Angiotensin II receptor blockers	966 (37.7)	15,140 (33.5)
Lipid-lowering drugs	1,505 (58.7)	25,829 (57.2)
Platelet aggregation inhibitors	879 (34.3)	15,080 (33.4)
Other antithrombotic agents	316 (12.3)	4,472 (9.9)
Opioids	799 (31.2)	12,389 (27.4)
Nonsteroidal anti-inflammatory drugs	1,135 (44.3)	17,939 (39.7)

Data are *n* (%) unless otherwise indicated.

95% CI 25.1–37.2) and for medullary thyroid cancer (PRR 28.7, 95% CI 16.1–51.1) (Fig. 2).

CONCLUSIONS

In this nationwide population-based study, use of GLP-1 RA was found to be associated with higher risk of thyroid cancer. Our results suggest that thyroid cancer risk should be considered with GLP-1 RA, particularly in patients treated for 1–3 years. Complementary pharmacovigilance analysis with use of the worldwide adverse drug reactions database provided consistent results.

To our knowledge, this is the first study with investigation of the risk of thyroid cancer with the main GLP-1 RAs in a large administrative database. Our findings are not consistent with those reported in the randomized controlled trials, which did not show an increase in risk of thyroid cancer with the different GLP-1 RA individually (7,16,17) or within a meta-analysis (8). However, these results were based on data from hyperselected patients from clinical trials with wide-ranging protocols far from real-life data and on very few observed cases of thyroid cancer (<10). In two other observational studies investigators did not find any risk of thyroid cancer with exenatide (9,10). However, these studies included use of commercial databases, inducing a risk of patient selection and, with far fewer exposed cases than in our study, probably lacked statistical power (<100 identified cases of thyroid cancer exposed or not to GLP1 RA in each study). Finally, results of our complementary pharmacovigilance global analyses were consistent with those of a U.S. pharmacovigilance study where exenatide was compared with other antidiabetes drugs and an excess reporting of thyroid cancers was found (18).

Several animal studies demonstrated that exenatide, liraglutide, and dulaglutide exposure was associated with medullary thyroid cancer in rodents of both sexes (2–6). The role of GLP-1 RA in increasing calcitonin release and upregulating calcitonin gene expression resulting in C-cell hyperplasia was thought to be specific to rodents (2,4). Our findings clearly raise concerns about the relevance of this risk to humans.

We found increased risk of thyroid cancer for all studied GLP-1 RA for >1 year of use, except for dulaglutide for 1–3 years of use, but the analysis was based on only 13 exposed cases (probably due to later marketing), suggesting a lack of statistical power in this group.

Although GLP-1 receptor expression in humans is lower than in rodents (2), GLP-1 receptors are present in human thyroid tissue or neoplastic thyroid C cells (19,20), suggesting a direct role of GLP-1 receptor activation in the occurrence of thyroid cancer in people with type 2 diabetes. In our study, the use of DPP-4 inhibitors was also found to be associated with higher risk of thyroid cancer but with lower risk estimates. These results can be related to the hypothesis that inhibition of DPP-4 results in increased endogenous GLP-1 levels but provides a lesser GLP-1 receptor activation than use of DPP-4–resistant direct RA.

Higher HRs were found for the period of 1–3 years of GLP-1 RA use (especially for male patients). Although the potential carcinogenic effect of GLP-1 RA on the thyroid is not well understood, this finding suggests either that induced thyroid cancers could develop after a relatively short period of GLP-1 RA exposure

Table 2—Adjusted HRs for association between use of GLP-1 RA or DPP-4 inhibitors and risk of all thyroid cancer or medullary thyroid cancer

	All thyroid cancer			Medullary thyroid cancer		
	Case subjects, *n* = 2,562	Control subjects, *n* = 45,184	Adjusted HR (95% CI)*	Case subjects, *n* = 398	Control subjects, *n* = 6,993	Adjusted HR (95% CI)*
Current exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
Past user	100 (3.9)	1,628 (3.6)	1.20 (0.96–1.50)	20 (5.0)	237 (3.4)	1.45 (0.84–2.50)
Current user	207 (8.1)	2,720 (6.0)	1.46 (1.23–1.74)	35 (8.8)	409 (5.9)	1.76 (1.16–2.69)
DPP-4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
Past user	387 (15.1)	6,462 (14.3)	1.07 (0.94–1.22)	66 (16.6)	999 (14.3)	1.12 (0.81–1.55)
Current user	653 (25.5)	11,316 (25.0)	1.10 (0.99–1.22)	101 (25.4)	1,777 (25.4)	1.15 (0.88–1.50)
Cumulative exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99–1.50)	23 (5.8)	278 (4.0)	1.57 (0.96–2.55)
1–3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27–1.95)	20 (5.0)	203 (2.9)	1.78 (1.04–3.05)
>3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05–1.74)	12 (3.0)	165 (2.4)	1.61 (0.85–3.06)
DPP-4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99–1.28)	58 (14.6)	798 (11.4)	1.33 (0.97–1.84)
1–3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84–1.10)	48 (12.1)	882 (12.6)	0.98 (0.69–1.39)
>3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04–1.35)	61 (15.3)	1,096 (15.7)	1.11 (0.79–1.55)

*Adjustment for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered by therapeutic class.

or that GLP-1 RA could promote thyroid precancerous lesions.

The presence of goiter, hypothyroidism, and hyperthyroidism was higher in case than in control subjects; hence, we adjusted for these variables in our analyses. It is unlikely that other slightly imbalanced characteristics such as hypertension or treatment by nonsteroidal anti-inflammatory drugs could have confounded the association. Importantly, we did not find evidence of a potential detection bias in the study herein presented. If such had existed, the risk of negative thyroidectomy (or thyroidectomy without associated thyroid cancer diagnosis) would have been found to be increased with GLP-1 RA use, which was not the case. This allows consideration that the increased cancer risk we report in our case-control analysis should not relate to the incidental finding of cancer in patients who would have been more likely to receive exploratory thyroidectomy. Additionally, screening bias is specifically expected for asymptomatic conditions, which is rarely the case for thyroid cancers, especially medullary ones. Similar to the detection bias, a reporting bias can occur in pharmacovigilance database analysis, which results from the preferential reporting of cases for drugs for which a risk or potential risk has already

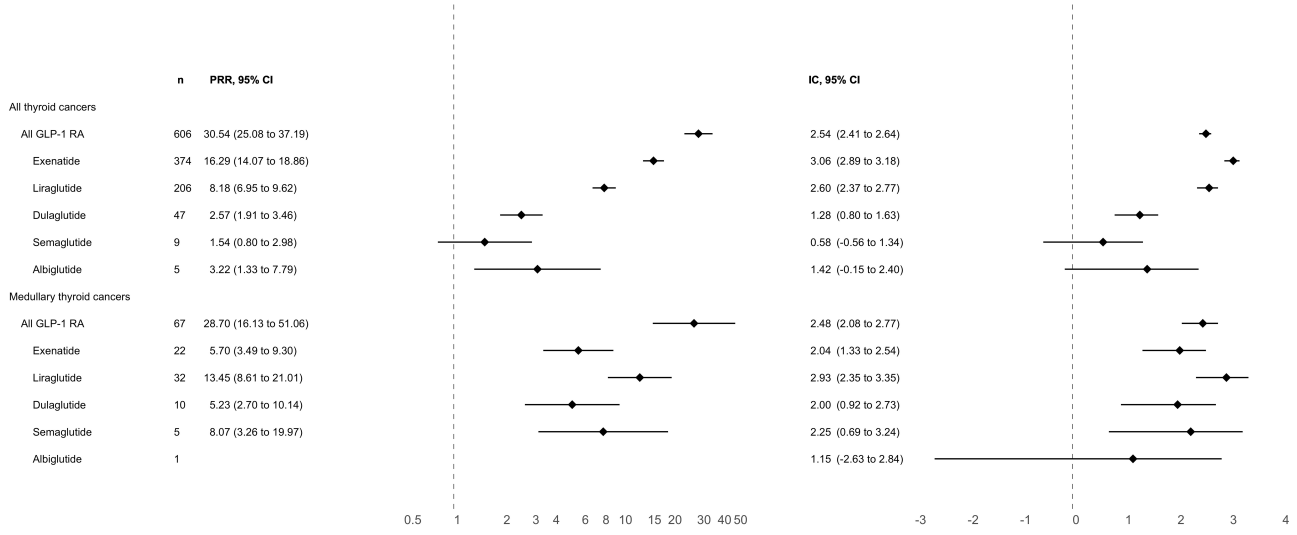

Figure 2—Disproportionality analyses of all thyroid cancer and medullary thyroid cancer with GLP-1 RA with use of the World Health Organization VigiBase PRR and IC. CI, confidence or credibility interval.

been communicated. As no warning regarding a potential signal associating GLP-1 RA with thyroid cancer had been emitted at the time the period we considered for the analysis ended, there is no reason to believe such bias would have affected the results of the complementary pharmacovigilance analysis we performed.

This study has several strengths, including the use of a real-world nationwide health care database allowing representativeness of current clinical practice (all eligible French patients exposed to second-line antidiabetes drugs were considered) and exhaustiveness of the data in terms of exposure (all dispensings are captured in the database), hospitalization diagnoses, and clinical/surgical procedures. Moreover, matching of case and control subjects and adjusting our models allowed consideration of important potential confounders such as age, sex, duration of diabetes, social deprivation index, goiter, hypothyroidism, hyperthyroidism, and exposure to other antidiabetes drugs. Included patients had at least 8 years of history in the database before the index date, allowing us to optimize assessment of diabetes duration. Finally, the results remained consistent in stratified and sensitivity analyses.

Nevertheless, this study has some limitations. First, definition of events and conditions with use of coded diagnoses and procedures in hospitalization databases cannot exclude misclassification of outcome and potential confounders. Moreover, there was no available specific code for medullary thyroid cancers. Hence, for this outcome, we used a definition combining a diagnosis of thyroid cancer with several calcitonin tests, CEA test, or a specific treatment (vandetanib) to improve the validity of case identification. Second, information on hospitalization diagnoses does not distinguish recurrent events with successive admissions from several hospitalizations related to a single incident event. However, exclusion of patients with a cancer in the 8 years prior to cohort entry probably prevented misclassification of incident events. Third, drug exposure assessed through use of health care databases is subject to misclassification since one cannot ascertained whether a dispensed drug is actually administered to the patient. Yet, several successive prescriptions are likely to be associated with actual drug use. Pharmacoepidemiological studies of cancer risk are often subject to protopathic bias. In our study, adding a lag time and analyzing its changes in sensitivity analyses reduced the impact of this potential bias. Finally, potential confounders such as family history of thyroid cancer and environmental radiation exposure were missing in the database, leading to the possibility of residual confounding, which is inherent to observational studies.

Conclusion

In summary, the results of this nationwide population-based study suggest that use of GLP-1 RA is associated with increased risk of thyroid cancer and medullary thyroid cancer in particular. The increased risk was higher for 1–3 years of GLP-1 RA use and remained elevated for >3 years of use. Clinicians should be aware of this potential risk in initiating a GLP-1 RA and carefully monitor exposed patients, especially in the presence of other risk factors for thyroid cancer.

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The opinions and conclusions in this study are not necessarily those of the various centers or of the World Health Organization.

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