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Meta-analysis

Association between glucagon-like peptide-1 receptor agonists and thyroid carcinoma; a systematic review and meta-analysis of observational studies

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Abstract

Introduction: Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are drugs administered to treat type 2 diabetes mellitus; however, their relationship with thyroid cancer is still unclear. Hence, the present study aimed to examine the association between the use of GLP1-RA and thyroid carcinoma.

Materials and Methods: Databases searched—including Web of Science, Cochrane, Scopus, ProQuest, PubMed, Embase, and Google Scholar—were searched without a time limit until May 1, 2025. Data were entered into SPSS 19 and analyzed using STATA 14. Tests with *P* values less than 0.05 were considered statistically significant ($P < 0.05$).

Results: The relationship between GLP1-RA and thyroid carcinoma based on hazard ratio (HR: 1.14, 95% CI: 0.86, 1.51) and incidence rate ratio (IRR: 1.32, 95% CI: 0.79, 2.20) was statistically insignificant. However, according to odds ratio (OR), use of GLP1-RA increased the risk of thyroid cancer (OR: 1.46, 95% CI: 1.23, 1.74). Furthermore, the association between GLP1-RA and medullary thyroid carcinoma was insignificant (HR: 1.51, 95% CI: 0.90, 2.54). The relationship between GLP1-RA and thyroid carcinoma among women (HR: 1.01, 95% CI: 0.69, 1.47), men (HR: 0.72, 95% CI: 0.33, 1.57), individuals aged 50 to 59 (HR: 1.30, 95% CI: 0.96, 1.75), 60 to 69 (HR: 0.95, 95% CI: 0.65, 1.38), in China (HR: 1.26, 95% CI: 0.91, 1.76), France (HR: 3.43, 95% CI: 1.30, 9.04), and Korea (HR: 1.05, 95% CI: 0.76, 1.46) was statistically insignificant. However, in the USA (HR: 1.44, 95% CI: 1.22, 1.71), GLP1-RA administration increased the risk of thyroid neoplasm.

Conclusion: Generally, the relationship between the GLP1-RA use in patients with type 2 diabetes mellitus and the risk of thyroid carcinoma was insignificant.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD420251051827) and Research Registry (reviewregistry1993) websites.

Keywords: Thyroid cancer, Glucagon-like peptide-1 receptor agonists, GLP 1R agonists, Thyroid adenoma, GLP-1 analogs, Incretin mimetics, Thyroid neoplasms, Thyroid carcinoma

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Introduction

Incretin-based treatments, including glucagon-like peptide-1 receptor agonists (GLP1-RAs) and DPP-4 inhibitors, are usually administered in combination to achieve goals such as glycemia, minimizing weight gain, inducing weight loss, or preventing cardiovascular diseases in type 2 diabetes mellitus patients (1). GLP1-RAs like exenatide, liraglutide, dulaglutide, and semaglutide are medications effective for treating type 2 diabetes (2), obesity, cardiovascular, renal, and hepatic steatosis (1,3-5). Since the approval of GLP1-RAs, a high administration rate for this type of drug has been reported for patients

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Implication for health policy/practice/research/medical education

In this meta-analysis, we found no statistically significant relationship between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in type 2 diabetes patients and the risk of thyroid carcinoma.

with type 2 diabetes (6). However, there are concerns over the adverse outcomes of GLP1-RAs use (7,8), such as gastrointestinal disorders and thyroid diseases (9,10), as according to the Food and Drug Administration of the United States, the spontaneous reporting rates of pancreatic and thyroid cancers with exenatide compared with other oral anti-diabetes medications were 2.9 and 4.7 times higher, respectively (11).

The hypothesis that GLP1-RAs may increase the risk of thyroid carcinoma is biologically acceptable (12,13). Recent research has reported GLP-1 receptors in human papillary thyroid cancer cells, causing the concern that the relationship amid GLP1-RA and thyroid malignancy may be beyond the medullary cancer and develop into other types of thyroid neoplasm (12-15). On the other hand, the relationship between obesity and increased risk of malignancy is confirmed, and since GLP1-RA use can reduce obesity, it may even play a role in reducing the cancer risk (16). Accordingly, the association between GLP1-RAs and thyroid cancer is unclear, as investigations (17,18) did not find a statistically significant relationship between GLP1-RAs and thyroid carcinoma (17,18). Whereas, other studies (19,20) demonstrated that GPA1-RA administration increased the risk of thyroid neoplasm. Hence, the present study examined the relationship between GLP1-RA and thyroid cancer using the systematic review and meta-analysis methods.

Materials and Methods

Study design

This research was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (21), and its protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) and Research Registry websites .

Search strategy

The databases Web of Science, Cochrane, Scopus, ProQuest, PubMed, Embase, and Google Scholar Search Engine were searched for studies published up to May 1, 2025, without any limitations on time or location. The Medical Subject Headings (MeSH) keywords and their equivalents were used in the search strategy, and the operators (AND, OR) were used to combine the keywords. The strategy included a manual search. The search strategy in the Scopus database was as follows: (TITLE-ABS-KEY (Glucagon-Like Peptide-1 Receptor Agonists OR GLP 1R Agonists OR GLP-1 Analogs OR incretion Mimetics) AND TITLE-ABS-KEY (Thyroid Neoplasms OR Thyroid Cancer OR Thyroid Carcinoma OR Thyroid Adenoma))

PICO (population, intervention, comparison, outcomes)

Our target population included observational studies that investigated the relationship between GLP1-RA use and thyroid carcinoma. GLP1-RA drug use was the intervention, and the comparison group included diabetic patients who did not use GLP1-RA. Investigating the relationship between GLP1-RA and the risk of thyroid carcinoma was the primary outcome.

Inclusion criteria

Observational studies that examined the association between GLP1-RA and thyroid carcinoma.

Exclusion criteria

Studies accepted temporarily; non-observational research; reviews; low-quality studies; duplicate studies and those conducted on thyroid cancer patients instead of diabetic patients; research that did not examine the relationship between GLP1-RA use and the general risk of cancer; studies without accessible full text, those that lacked sufficient data, and studies presented in congresses.

Quality assessment

Two researchers evaluated the quality of articles using the Newcastle-Ottawa Scale. Except for the comparison item, each question received a maximum of one star. Accordingly, the lowest score was zero (indicating the lowest quality) and the highest was 10 (showing the highest quality). Articles with scores lower than six were considered low quality (22).

Data extraction

Two researchers independently extracted data, including age, type of study, sample size, country of origin, publication year, author's name, the relationship between GLP1-RA use and thyroid malignancy, in addition to the 95% confidence interval (in the general population, male, and female patients). Then, the two researchers addressed the discrepancies through the understanding solution.

Statistical analysis

Logarithms of odds ratio (OR), hazard ratio (HR), and incidence rate ratio (IRR) were used for data analysis, and the studies were combined. The I2 index was used to assess the heterogeneity between studies. The studies were combined using a random effects model. Additional analyses included meta-regression, publication bias, and sensitivity analysis. Data were entered into SPSS 19 and analyzed using STATA 14. Tests with P values lower than 0.05 were considered statistically significant ($P<0.05$).

Results

In total, 399 articles were found in the search stage, and 161 of them were identified as duplicates and were removed.

The abstracts were reviewed and four studies that lacked full text were dismissed. From the remaining 234 articles, 84 lacked the required data for analysis and were removed. Among the 150 studies that entered the next stage, 140 were withdrawn due to other exclusion criteria and 10 articles remained (Figure 1).

The current study reviewed 10 observational studies (nine cohort and one case-control) (Table 1).

According to the analysis based on the index (Figure 2), the relationship between GLP1-RA use and thyroid malignancy based on HR (HR: 1.14, 95% CI: 0.86, 1.51) and IRR (RR: 1.32, 95% CI: 0.79, 2.20) was insignificant. However, based on OR, GLP1-RA use increased the risk of thyroid cancer (OR: 1.46, 95% CI: 1.23, 1.74). Since only the reports of one study were based on OR, this outcome requires further examination.

According to Table 2, subgroup analysis revealed that patients' sex and age had no effect on the relationship between GLP1-RA use and thyroid carcinoma, and the association between GLP1-RA and medullary thyroid malignancy was insignificant. Furthermore, the relationship between GLP1-RA and thyroid malignancy in China, France, and Korea was statistically insignificant. However, in the USA, GLP1-RA use increased the risk of thyroid neoplasm (HR: 1.44, 95% CI: 1.22, 1.71). The relationship between GLP1-RA and thyroid carcinoma in cohort studies was insignificant. In the case-control study, on the other hand, GLP1-RA administration increased the risk of thyroid carcinoma (HR: 3.43, 95% CI: 1.30, 9.04).

Meta-regression demonstrated that there was no statistically significant relationship between the "association between GLP1-RA and thyroid carcinoma" and the publication year of the studies ($P = 0.183$) or the number of study samples ($P = 0.645$; Figures 3 and 4).

According to Figure 5, publication bias diagram showed that there was no publication bias in the current research ($P = 0.880$). Hence, the studies with negative and positive results had the chance to be published and were covered in the search stage.

Sensitivity analysis revealed that Levy et al (19) and Pasternak et al (24) studies were the most effective on the general outcome of the present meta-analysis; as removing

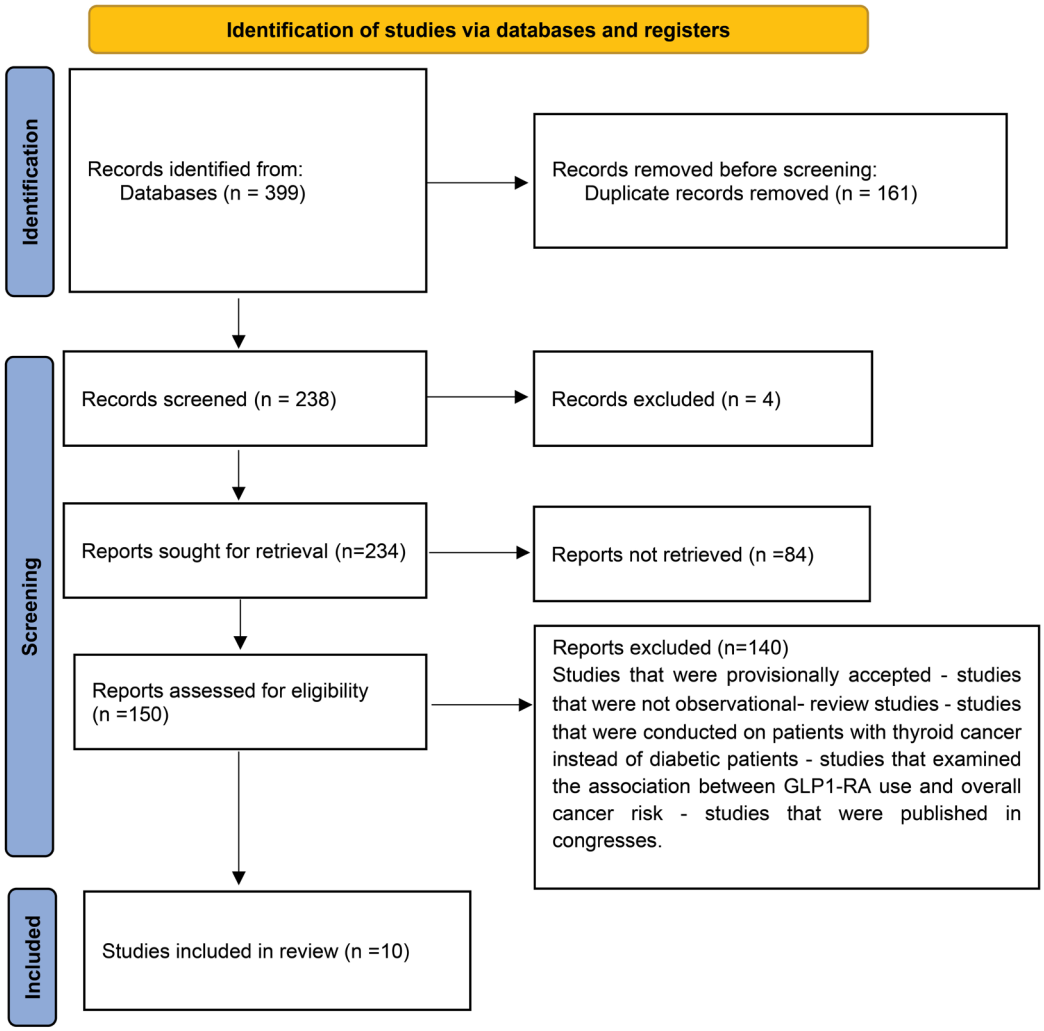

Figure 1. The PRISMA flow chart of study selection.

Table 1. Summarized information of the studies

Author, year	Index	Country	Type of study	Duration of study	Number of samples in the GLP1-RA group	Mean age in the GLP1-RA group (year)	Number of samples in the comparison group	Mean age in the comparison group (year)	Comparison group
Baxter SM, 2025 (17)	HR	Canada, Denmark, Norway, South Korea, Sweden, Taiwan	Cohort	2007-2023	98147	62	2488303	62	DPP-4i
Brito JP, 2025 (18)	HR	USA	Cohort	2014-2021	41110	65.14	306579	65.38	DPP4i, SGLT2i, Sulfonylurea
Bea S, 2024 (23)	HR	Korea	Cohort	2014-2020	21722	57.1	326993	56.1	SGLT2i
Pasternak B, 2024 (24)	HR	Sweden, Denmark, Norway	Cohort	2007-2021	145410	57.5	291667	63.5	DPP-4i
Levy S, 2024 (19)	HR	USA	Cohort	2013–2023	206845	50	912878	49.7	Non-user
Kim M, 2024 (25)	IRR	Korea	Cohort	2004-2021	2609	51.5	2609	50.9	Non-user
Cheng Z, 2024 (26)	HR	China	Cohort	2016-2022	7383 7680	NR NR	13827 15163	NR NR	Insulin Metformin
Bezin J, 2023 (27)	HR	France	Case-control	2014-2018	2562	64	45184	64	Non-user
Wang J, 2022 (20)	OR	USA	Cohort	2005-2019	64230	NR	619340	NR	Metformin
Strand MW, 2025 (28)	HR	USA	Cohort	2012-2025	4912	58	82964	62.5	Metformin

NR: Not reported; OR: Odds ratio, HR: Hazard ratio, IRR: incidence rate ratio, DPP-4i: Dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium-Glucose Transport Protein 2 Inhibitors.

each of them would drastically change the final outcome (Figure 6).

Discussion

Generally, there was no statistically significant relationship between GLP1-RA in type 2 diabetes patients and the risk of thyroid cancer. In a previous meta-analysis by Silveri et al on RCT studies, GLP1-RA increased the risk of thyroid neoplasm (Mantel-Haenszel odds ratio [MH-OR]: 1.52, 95% CI: 1.01, 2.29). However, there was no statistically significant relationship between GLP1-RA and papillary thyroid cancer (MH-OR: 1.54, 95% CI: 0.77, 3.06) or medullary thyroid cancer (MH-OR: 1.44, 95% CI: 0.23, 9.16), which was consistent with our study, but there

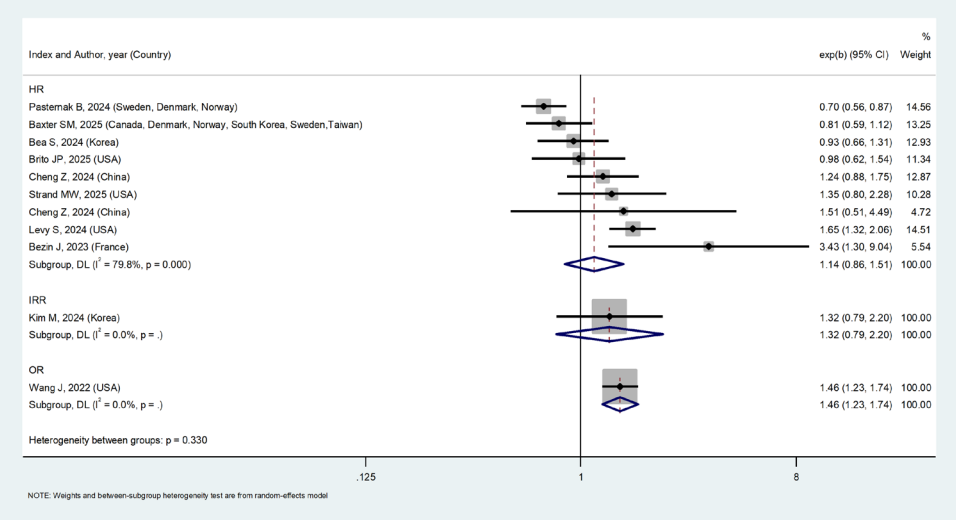

Figure 2. Forest plot showing the association between GLP-1 RA and thyroid carcinoma by index.

Table 2. Association between GLP-1RA use and thyroid carcinoma based on subgroups studied

Subgroups		OR/HR/IRR	Low	Up	I^2 (%)	*P* value
Sex	Male	0.72	0.33	1.57	53.5	0.116
	Female	1.01	0.69	1.47	59.1	0.087
Age group (year)	50-59	1.30	0.96	1.75	60.4	0.056
	60-69	0.95	0.65	1.38	72.4	0.013
Country	Korea	1.05	0.76	1.46	19.4	0.265
	USA	1.44	1.22	1.71	28.9	0.238
	China	1.26	0.91	1.76	0	0.736
	France	3.43	1.30	9.04	0	-
Type of study	Cohort	1.13	0.89	1.42	79.7	<0.001
	Case-control	3.43	1.30	9.04	0	-
Type of cancer	Medullary thyroid cancer	1.51	0.90	2.54	11.9	0.321

OR: Odds ratio, HR: Hazard ratio, IRR: incidence rate ratio.

were differences (29). Unlike the current meta-analysis, the mentioned meta-analysis reported a significant association between GLP1-RA use and thyroid carcinoma. Since the previous meta-analysis was conducted on RCTs and the present meta-analysis reviewed the observational studies, the difference between the examined studies may be the reason for the variation in the final outcomes of the meta-analyses.

In the systematic review by Feier et al, the occurrence of thyroid cancer in patients under treatment with semaglutide was lower than 1%, which indicated the insignificance of the risk (30). In a meta-analysis by Hu et al, GLP1-RA use had no relationship with the risk of general thyroid disorders (RR: 1.28, 95% CI: 1.03, 1.60) and thyroid carcinoma (RR: 1.30, 95% CI: 0.86, 1.97) (31). In research by Sun et al, the association between GLP1-RA and ovary (OR: 0.99, 95% CI: 0.90, 1.09), lung (OR:

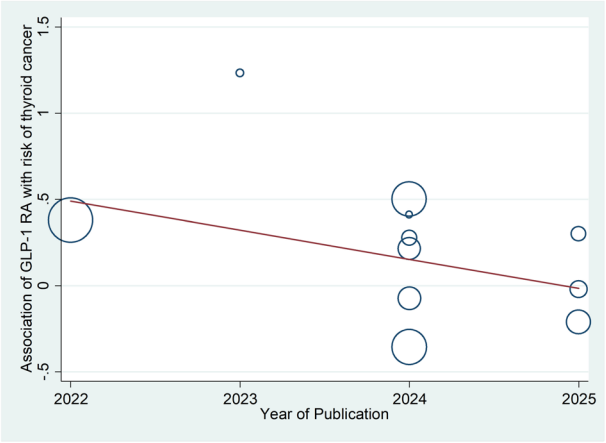

Figure 3. Meta-regression of the relationship between GLP-1 RA and thyroid carcinoma by year.

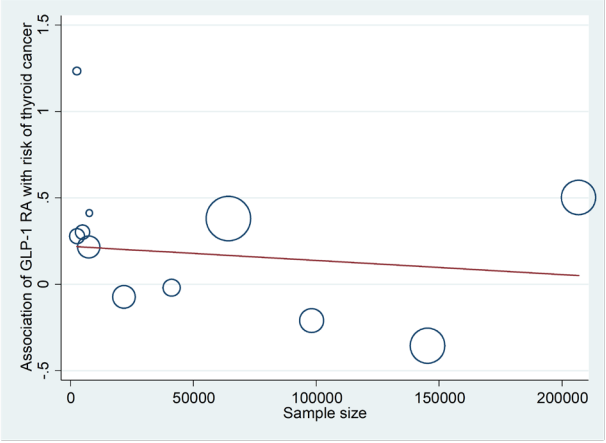

Figure 4. Meta-regression of the relationship between GLP-1 RA and thyroid carcinoma by sample size.

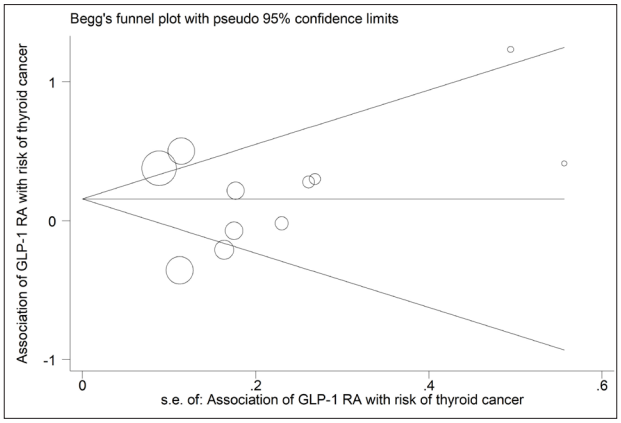

Figure 5. Diagram of publication bias.

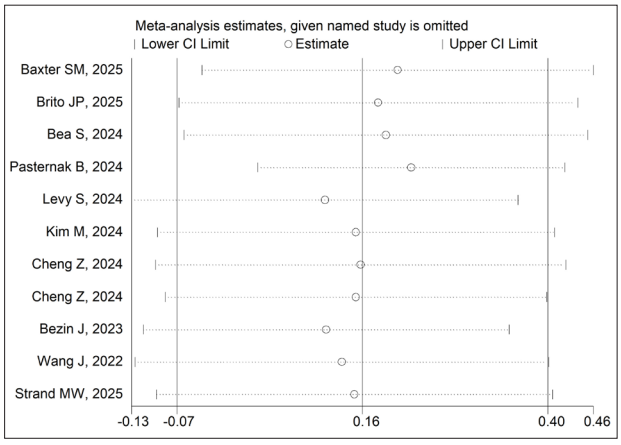

Figure 6. Sensitivity analysis.

1.01, 95% CI: 0.93, 1.10), and thyroid (OR: 0.83, 95% CI: 0.63, 1.10) cancers was statistically insignificant (32). According to the results of a meta-analysis by Cao et al, there was no significant relationship between GLP1-RAs and the general risk of cancer (RR: 1.03, 95% CI: 0.95, 1.12), thyroid carcinoma (OR: 1.49, 95% CI: 0.83, 2.66), and pancreatic neoplasm (33). The findings of these studies confirmed the result of our study, indicating that there was no significant relationship between GLP1-RA and thyroid carcinoma.

According to the meta-analysis by Figlioli et al on RCTs, there was no statistically association between GLP1-RA and the general risk of gastrointestinal (RR=0.99, 95% CI: 0.86, 1.13), liver (RR=0.79, 0.51, 1.21), esophageal (RR=0.70, 0.38, 1.28), gallbladder (RR=1.32, 0.43, 4.00), pancreas (RR=1.05, 0.77, 1.43), small intestine (RR=0.78, 0.20, 3.04), and stomach (RR=0.88, 0.58, 1.33) cancers (34). In a recent meta-analysis by Pinto et al, the relationship between GLP1-RA and the risk of pancreatic neoplasm was statistically insignificant compared with other treatments (OR: 1.06; 95% CI: 0.67, 1.67) (35). The recent meta-analysis by Liu et al, GLP1-RA administration did not increase the risk of malignant neoplasia compared with the placebo or other interventions (OR: 1.04, 95% CI: 0.94, 1.15) (36). The mentioned articles were consistent with this study, and they believed that there was no relationship between GLP1-RA use and the risk of gastrointestinal, lung, and ovarian cancers.

Sun et al reported that GLP1-RA use was associated with a decrease in the risk of breast cancer (OR: 0.92, 95% CI: 0.88, 0.96) and an increased risk of colon cancer (OR: 1.12, 95% CI:1.07, 1.18) (32). Meanwhile, the meta-analysis conducted by Shabil et al showed that GLP1-RA treatment reduced the risk of liver cellular carcinoma compared with the comparison group (HR: 0.41, 95% CI: 0.28, 0.55) (37). Sharma et al conducted a meta-analysis and reported that GLP1-RA treatment decreased the risk of prostate carcinoma (RR: 0.72, 95% CI: 0.61, 0.83) (38). These studies were not consistent with the present meta-analysis, as they indicated that the connection between GLP1-RA and the incidence of several cancers (breast, prostate, liver cellular carcinoma, and colon) was statistically significant. However, considering the variety of the examined cancers, the discrepancies between the results may be due to the differences in the type of examined cancer.

Conclusion

There was no statistically significant relationship between the GLP1-RA use and the risk of thyroid carcinoma. Furthermore, the age and sex of the patients did not affect the association between GLP1-RA and thyroid neoplasm. The relationship between GLP1-RA and medullary thyroid cancer was statistically insignificant. Considering the limited number of reviewed studies, it appears that more observational studies are necessary on this issue to examine various dimensions of the relationship between GLP1-RA use and thyroid cancer.

Limitations of the study

(a) The reviewed articles did not mention the type of GLP1-RA; hence, subgroup analysis based on the GLP1-RA type was not possible. (b) The number of studies was limited, and the administered drugs to the comparison groups were diverse. Accordingly, it was not possible to compare the GLP1-RA and other antidiabetic medications, and their effect on thyroid cancer occurrence. (c) Only one of the reviewed studies was case-control. (d) The examined articles reported their results based on three different indices (i.e., OR, HR, and IRR).

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Authors' contribution

Conceptualization: Mahmoud Dehghani-ghorbi and Mahsa Ebrahimi.
Data curation: Sajad Ataei Azimi and Maedeh Seifollahi Marbini.
Formal analysis: Mahboobeh Akhondi and Mojtaba Lotfi.
Investigation: Mahmoud Dehghani-ghorbi and Mehrnaz Nazari Rad.
Methodology: Mahboobeh Akhondi and Mehrangiz Ghafari.
Project management: Sajad Ataei Azimi.
Supervision: Mahmoud Dehghani-ghorbi.
Validation: Mehrangiz Ghafari and Mojtaba Lotfi.
Visualization: Mahsa Ebrahimi and Seyed Amir Sheikholeslami.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD420251051827) and the Research Registry website with (Unique Identifying Number (UIN); reviewregistry1993). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the author.

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