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REVIEW

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Metabolic obesity phenotypes and thyroid cancer risk: A systematic exploration of the evidence

Mehdi Hedayati[1] | Majid Valizadeh[2] | Behnaz Abiri[2]

[1]Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
Behnaz Abiri, Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: abiri@sbmu.ac.ir

Abstract

Background: Obesity is recognized as a risk factor for various cancers, including thyroid cancer. However, the association between different metabolic obesity phenotypes and thyroid cancer risk remains unclear. This systematic review aimed to comprehensively evaluate the existing literature to elucidate the association between metabolic obesity phenotypes and thyroid cancer risk.

Methods: This systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Scopus, EMBASE, Web of Science, and Google Scholar were searched for relevant studies until April 2024. Studies examining the link between metabolic obesity phenotypes and thyroid cancer risk were included.

Results: Five cohort studies involving 831,510 participants met the inclusion criteria. Metabolically unhealthy obesity was consistently associated with an increased risk of thyroid cancer in both men and women. Central adiposity emerged as a significant predictor of thyroid cancer risk. Mechanistically, chronic inflammation, dysregulated adipokine secretion, hormonal imbalances, and altered signaling pathways may contribute to thyroid carcinogenesis. There is an ongoing debate regarding the risk associated with metabolically healthy obesity, with some suggesting potential protective effects due to favorable metabolic profiles.

Conclusion: This systematic review highlights the complex relationship between metabolic obesity phenotypes and thyroid cancer risk. The findings highlighted the importance of considering metabolic status alongside obesity in thyroid cancer risk assessment and intervention strategies.

KEYWORDS
cancer risk, metabolic obesity phenotypes, obesity, thyroid cancer

1 | INTRODUCTION

Obesity has been identified as a recognized risk factor for various types of cancer, including breast, endometrial, colon, and prostate cancers, indicating its potential impact on cancer occurrence.[1–4] Previous epidemiological studies and meta-analyses of prospective cohorts have also demonstrated a link between obesity and the risk of thyroid cancer.[4–7] Although the precise mechanisms linking obesity to thyroid cancer remain unclear, researchers suggested that metabolic abnormalities associated with obesity may play a role in mediating this connection.[8,9] However, there is variability in the prevalence of metabolic disturbances associated with obesity among the affected individuals. In fact, some individuals with obesity, known as metabolically healthy individuals, have garnered attention for exhibiting a favorable metabolic profile without metabolic abnormalities.[10–12] Thus, the four frequently defined metabolic obesity phenotypes are metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obese (MHO), and metabolically unhealthy overweight/obese (MUO).[13]

Various obesity phenotypes could provide insights into whether obesity itself or the co-existence of metabolic abnormalities contributes to a heightened risk of thyroid cancer. However, few studies have investigated the relationship between metabolic abnormalities and thyroid cancer risk among individuals with a normal BMI or those who are overweight or obese, and the results have been inconsistent. Therefore, it remains unclear whether the risk of thyroid cancer varies among different metabolic obesity phenotypes.

Understanding the connection between metabolic obesity phenotypes and thyroid cancer risk has substantial clinical significance for risk assessment, preventive measures, and targeted interventions. Establishing whether the risk of thyroid cancer differs across various metabolic obesity phenotypes could assist in identifying high-risk populations that could benefit from enhanced surveillance or lifestyle modifications. In addition, elucidating the underlying mechanisms linking metabolic abnormalities to the development of thyroid cancer may reveal potential therapeutic targets. Thus, this systematic review endeavored to thoroughly assess the current literature to clarify the association between metabolic obesity phenotypes and thyroid cancer risk, illuminating the intricate interplay between obesity, metabolism, and thyroid cancer pathogenesis.

2 | MATERIAL AND METHODS

2.1 | Literature search and inclusion criteria

An extensive literature review was conducted by querying databases such as PubMed, Scopus, EMBASE, Web of Science, and Google Scholar up to April 2024. The search terms for obesity metabolic phenotype included obesity, obese, overweight, normal weight, metabolic, metabolically, healthy, unhealthy, benign, and phenotype. Those terms were combined with search terms for thyroid cancer, including thyroid carcinoma, thyroid cancer, thyroid neoplasms and thyroid tumor. The literature search was restricted to human studies published in English. Studies were considered potentially suitable if they met the following criteria: (i) were original observational studies and (ii) explored the link between metabolic obesity phenotypes and thyroid cancer. However, literature reviews, case-control studies, clinical trials, animal or genetic variation studies, and studies lacking reports of thyroid cancer events were excluded from consideration.

The process of selecting these studies is illustrated in Figure 1. Due to variations in participant characteristics, settings, and the diversity of statistical methods employed across the included studies as well as a lack of data amenable to pooling, a qualitative systematic review was conducted. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) Statement.[14]

Table 1 presents the PICOS (population, intervention/exposure, comparator, outcome, and setting) items used in the systematic review. Ethical approval was not required due to the methodological approach employed.

2.2 | Study selection

After removing duplicates, two authors (BA and MV) independently evaluated the titles and abstracts obtained from the initial search. Both authors (BA and MV) scrutinized full-text articles to verify their adherence to the inclusion and exclusion criteria. In instances of disagreement, a third author (MH) reassessed these issues.

2.3 | Data extraction and quality assessment

Data extraction was independently conducted by two reviewers (BA and MV) and any discrepancies were resolved through consensus. Information was extracted about the first author, year of publication, country, study design, follow-up duration, population, age, number of participants, study population, definition of metabolic phenotypes, and main findings.

The Newcastle-Ottawa Scale (NOS), a tool designed for assessing nonrandomized studies in systematic reviews and meta-analyses, was used.[15] The NOS consists of eight items that are divided into three categories: selection, comparability, and exposure. Each item in the NOS provides a response choice. The star system was used to semi-quantitatively evaluate the quality of the studies, assigning a maximum of 1 star per item to the highest quality studies. However, an exception is made for evaluating comparability, in which up to two stars can be awarded. Therefore, NOS operates on a scale of 0 to 9 stars.[16] The details of data extraction and quality assessment are presented in Table 2.

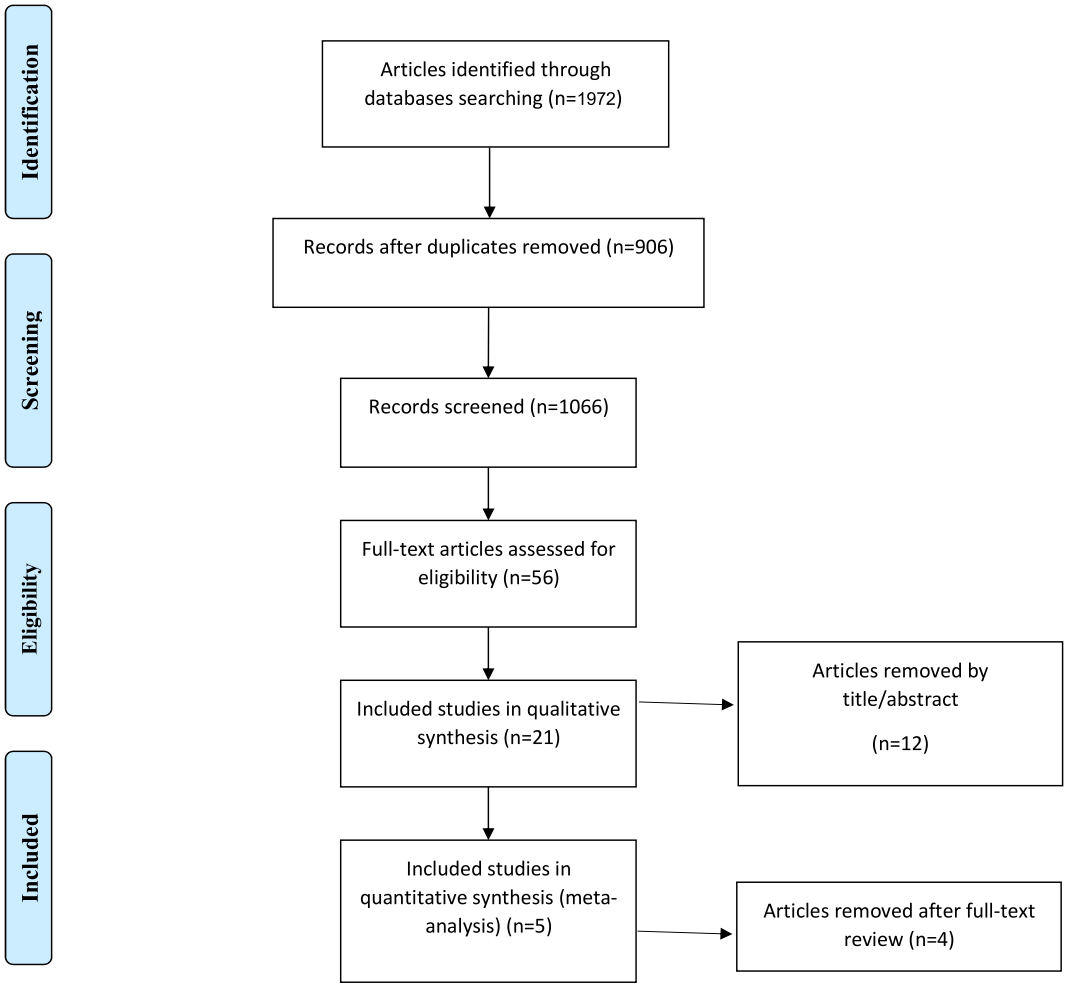

FIGURE 1 Flow chart of the process of the study selection.

TABLE 1 PICOS (population, intervention/exposure, comparator, outcome, and setting) criteria used to perform the systematic review.

PICOS	Criteria
Population	Healthy general population across all age groups
Intervention/exposure	Metabolic obesity phenotypes
Comparator	Comparison between different metabolic obesity phenotypes
Outcome	The risk or incidence of thyroid cancer among individuals classified into different metabolic obesity phenotypes
Setting	Observational studies

3 | RESULTS

3.1 | Literature search and study selection process

An initial search utilizing keywords pertinent to the topic resulted in 1972 full-text articles. Following the elimination of duplicate studies and the application of inclusion and exclusion criteria through two separate stages (title and abstract review), five eligible studies were included in the review. Therefore, five studies[9,17–20] with 831,510 participants in total (398,899 males and 432,611 females), published between 2019 and 2023, could be considered for the systematic review.

Figure 1 illustrates the flow chart for selecting studies.

3.2 | Study characteristics

Table 2 presents a summary of the various characteristics of the included studies. The sample size of the included studies ranged from 390,575 to 5734 participants. Studies were conducted in South

TABLE 2 Characteristics of the studies investigating the association between metabolic phenotypes and risk of thyroid cancer incidence.

First author, year (reference No)	Country	Study design	Follow-up duration	Sample size (M/F)	Age of participants	Study population	Definition of metabolic phenotype	Main finding	Study quality (NOS)
Winn, 2023[17]	United States	Cross-sectional	NA	19,500 (9624/9876)	≥18	Participants of the NHANES	The study defined metabolic phenotypes based on BMI and MetS criteria from the NCEP ATPIII. Three phenotypes were established: (1) broad, including individuals with ≥1 MetS criteria as metabolically unhealthy; (2) mild dysfunction, comprising those with 1–2 MetS criteria as unhealthy; and (3) traditional MetS definition, classifying individuals with ≥3 MetS criteria as unhealthy.	MUNW participants have a higher risk of ORC than other abnormal phenotypes, compared with MHNW participants.	7
Nguyen, 2022[18]	Korea	Cohort	Mean duration of 7.4 years	160,650 (55,252/105,398)	40–79	Participants of the KoGES, including the KoGES_Ansan and Ansung study, the KoGES_ CAVAS, and the KoGES_ HEXA.	Individuals with a BMI ≥ 25 kg/m^2 were considered obese. Metabolic abnormality was defined based on the presence of three or more unhealthy factors according to modified NCEP ATP III. Thyroid cancer risk was further analyzed by combining general obesity and central obesity or low HDL-cholesterol levels.	Metabolically unhealthy women or women with central adiposity may be at an increased thyroid cancer risk despite normal BMI.	8
Lin, 2021[19]	Taiwan	Cohort	Median period of 13.7	5734 (5034/700)	≥20	Participants of the Taiwan national health interview survey 2001	The study categorized participants based on their BMI into underweight (BMI < 18.5), normal weight (BMI 18.5–23.9), overweight (BMI 24–26.9), and obese (BMI ≥ 27) groups using Taiwanese-specific criteria. Those without cardiometabolic diseases and with a healthy cardiometabolic blood profile were considered metabolically healthy.	Compared to the participants with MHNW, participants with MHOW or MHO had a tendency toward a higher risk of cancer, including thyroid cancer. These associations were stronger in MHOW or MHO participants younger than 65 years. Even in the absence of metabolic abnormalities, overweight, and obesity may cause a modest increase in the risk of developing cancer.	6

TABLE 2 (Continued)

First author, year (reference No)	Country	Study design	Follow-up duration	Sample size (M/F)	Age of participants	Study population	Definition of metabolic phenotype	Main finding	Study quality (NOS)
Cao, 2020[20]	UK	Cohort	Median of 7.8 years	390,575 (183,621/206,954)	40–69	General population of the UK biobank study	The study classified participants by BMI into obesity, overweight, and normal weight categories, using ATP-III criteria to identify MetS. Those meeting two or more criteria were considered to have MetS. Participants were grouped into six phenotypes based on their BMI and MetS status. Sensitivity analyses examined various criteria for defining metabolic health.	The MU-OW phenotype was associated with increased risk of thyroid cancer. The study found no association between obesity and thyroid cancer in either metabolically healthy or metabolically unhealthy individuals.	8
Kwon, 2019[9]	South Korea	Cohort	The median period of 5.3 years	255,051 (145,368/109,683)	>18	Participants of the Kangbuk Samsung health study.	BMI categories ranged from underweight (BMI <18.5 kg/m^2) to obese (BMI ≥ 25 kg/m^2). Metabolically unhealthy individuals had at least one of the following: FBS ≥ 100 mg/dL, BP ≥ 130/85 mmHg, TG ≥ 150 mg/dL, HDL-C < 40 mg/dL in men or < 50 mg/dL in women, or HOMA-IR score ≥2.5, or were on relevant medications. Otherwise, being metabolically healthy meant having none of these abnormalities.	In both MH and MUH men, obesity was associated with an increased risk of incident thyroid cancer. Conversely, women with MUH obesity, but not MH obesity, were found to have an increased risk of thyroid cancer.	8

Abbreviations: BMI, body mass index; BP, blood pressure; CAVAS, Cardiovascular Disease Association Study; FBS, fasting blood sugar; HEXA, Health Examinee Study; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; KoGES, Korean Genome and Epidemiology Study; MetS, metabolic syndrome; MH, metabolically healthy; MHNW, metabolically healthy normal weight; MUH, metabolically unhealthy; MUNW, metabolically unhealthy normal weight; MU-OW, metabolically unhealthy overweight; NCEP, National Cholesterol Examination Program; NHANES, National Health and Nutrition Examination Survey; NOS, Newcastle–Ottawa Scale; ORC, obesity-related cancer.

Korea,[9] USA,[17] UK,[20] Taiwan,[19] and Korea.[18] The median follow-up duration ranged from 5.3 to 13.7 years across the included studies. All the studies included in the review involved participants of both sexes. All participants included in this systematic review were aged ≥18 years. Four of the studies were cohort studies, and one was a cross-sectional study.[17]

The included studies predominantly considered the following potential confounding variables: age, sex, race/ethnicity, center of treatment, year of screening exam, alcohol intake, smoking, physical activity, daily hours sedentary, level of education, income, marital status, daily calorie intake, survey year, menopausal status (for women), undergoing menopausal hormone therapy, duration of

thyroid cancer diagnosed, total cholesterol, HDL-C, triglycerides, glucose, systolic blood pressure, hsCRP, HOMA-IR, TSH.

3.3 | The association between obesity phenotypes and risk of thyroid cancer

A cohort study by Kwon et al.[9] examined the association between BMI, metabolic health status, and thyroid cancer risk among 255,051 adults categorized as metabolically healthy or metabolically unhealthy. Based on the study results, among men, the multivariable-adjusted hazard ratio (HR) (95% confidence interval [CI]) for thyroid cancer when comparing obesity (defined as BMIs of ≥25 kg/m^2) with a BMI of 18.5–22.9 kg/m^2 was 1.47 (1.12–1.93) in metabolically healthy individuals, while the corresponding HR (95% CI) in metabolically unhealthy individuals was 1.26 (1.03–1.53). For women, the corresponding multivariable-adjusted HR (95% CI) in metabolically healthy individuals was 1.50 (0.80–1.36), while in metabolically unhealthy individuals, it was 1.43 (1.22–1.69). Elevated quartiles of waist circumference showed a positive correlation with thyroid cancer risk in both metabolically unhealthy men and women (*P* for trend <0.005), whereas no such association was observed in metabolically healthy participants. Therefore, the authors concluded that in both metabolically healthy and metabolically unhealthy men, obesity is linked to a higher risk of developing thyroid cancer, suggesting that excessive adiposity itself serves as an independent risk factor for thyroid cancer. In contrast, women with metabolically unhealthy obesity but not metabolically healthy obesity demonstrated an elevated risk of thyroid cancer. This suggests that obesity accompanied by metabolic abnormalities might influence thyroid cancer risk, specifically in women.

In a study utilizing data from 173,343 participants in the Korean Genome and Epidemiology Study, Nguyen et al.[18] found that metabolically unhealthy women, regardless of weight status, exhibited a higher risk of thyroid cancer than non-obese women without metabolic abnormalities. The HR with 95% CI was 1.57 (1.02–2.40) for normal-weight women and 1.71 (1.21–2.41) for obese women. No significant association was observed among the men. Non-obese women with a high waist circumference (≥85 cm) had a higher risk of thyroid cancer (HR 1.62, 95% CI 1.03–2.56) compared with those with a low waist circumference. Similarly, obese women with low HDL-cholesterol (<50 mg/dL) had a higher risk of thyroid cancer (HR 1.75, 95% CI 1.26–2.42) compared with non-obese women with high HDL-cholesterol. Therefore, their conclusion suggests that metabolically unhealthy women or those with central adiposity may have an elevated risk of thyroid cancer even with a normal BMI.

A study conducted by Winn et al.[17] investigated the relationship between metabolic obesity phenotypes and the risk of obesity-related cancer (ORC) among participants in the NHANES dataset. ORCs encompassed breast, colorectal, uterine, ovarian, pancreatic, liver, gallbladder, kidney, and thyroid cancer. The findings revealed that ORC cases (n = 528) showed higher proportions of MUNW (28.2% vs. 17.4%) and MUO (62.6% vs. 60.9%) phenotypes than cancer-free individuals (n = 18,972). Compared to MHNW participants, MUNW participants exhibited a 2.2-times higher ORC risk [OR (95%CI) = 2.21 (1.27–3.85)]. Although MHO and MUO participants showed 43% and 56% increased ORC risk, respectively, compared with MHNW, these differences did not reach statistical significance [OR (95% CI) = 1.43 (0.46–4.42), 1.56 (0.91–2.67), respectively]. Hence, individuals with the metabolically unhealthy normal weight (MUNW) phenotype exhibit a greater susceptibility to obesity-related cancers (ORC) than those with other abnormal phenotypes, when compared to metabolically healthy normal weight (MHNW) participants.

In another study conducted by Cao et al.,[20] utilizing data from individuals aged 37–73 years in the UK Biobank enrolled between 2006 and 2016, with a median follow-up duration of 7.8 years, researchers revealed that the metabolically unhealthy overweight (MU-OW) phenotype was associated with elevated risks of certain site-specific cancers, including thyroid cancer.

In a nationwide, representative community-based prospective cohort study, Lin et al.[19] examined 5734 Taiwanese adults and categorized them into eight phenotypes based on BMI and metabolic status (healthy/unhealthy). They found that participants categorized as MHOW (adjusted HR 1.39, 95% CI, 0.90–2.13) or MHO (adjusted HR 1.07, 95% CI, 0.51–2.22) tended to have a slightly elevated risk of cancer, including thyroid cancer, compared to those with metabolically healthy normal weight. These associations were more pronounced among MHOW (adjusted HR 1.77, 95% CI, 1.09–2.86) or MHO (adjusted HR 1.39, 95% CI, 0.66–2.93) participants younger than 65 years.

4 | DISCUSSION

The findings of this systematic review demonstrated a complex relationship between obesity phenotypes and the risk of thyroid cancer. Several key themes emerge from the synthesis of the included studies, shedding light on the nuanced interplay between obesity, metabolic health, and thyroid cancer risk.

The results from the included studies collectively suggested that obesity, particularly when accompanied by metabolic abnormalities, may contribute to an elevated risk of thyroid cancer. This aligns with the broader body of literature indicating a positive association between obesity and various cancers, including thyroid cancer.

Prior research has shown a connection between obesity, as determined by BMI, and the risk of thyroid cancer.[4–7] Obesity is defined as an abundance of adipose tissue and often coincides with metabolic complications, including elevated blood sugar levels, high blood pressure, abnormal lipid levels, and resistance to insulin[12]. An irregular metabolic state is associated with an increased risk of thyroid cancer.[8,21,22] A cohort study conducted on a population basis revealed a negative correlation between blood glucose levels and the occurrence of thyroid cancer among women.[22] In another case-control study, researchers found that 20 women diagnosed with differentiated thyroid cancer exhibited a higher prevalence of insulin

resistance than control subjects who were matched for age, sex, and BMI.[8] Nevertheless, it remains unclear whether the heightened risk of thyroid cancer is directly linked to obesity itself or to the presence of accompanying metabolic abnormalities.[8,21,22] This uncertainty arises because many previous studies have assessed the relationship between BMI and thyroid cancer risk without accounting for metabolic status, which is typically associated with obesity.[4–7]

The sex-specific trends noted in the correlation between obesity and the risk of thyroid cancer underscore the potential variations in susceptibility and underlying mechanisms between males and females. Sex-specific variations in fat distribution can influence the onset of thyroid cancer. Men typically accumulate fat around the visceral region, whereas women primarily store fat in the gluteal-femoral area.[23] Moreover, recent research examining the distinct functions of upper- and lower-body fat in metabolism has indicated the potential protective effects of lower-body fat on certain diseases.[24,25]

Moreover, the importance of central adiposity, as reflected by waist circumference, in predicting the risk of thyroid cancer[9] emphasizes the necessity of incorporating measures of central obesity along with BMI when evaluating cancer risk.

Potential mechanisms have been identified to elucidate the association between obesity and the development of thyroid cancer via metabolic dysregulation. Chronic low-grade inflammation augments the generation of reactive oxygen species, accelerates the cell cycle, and diminishes the function of tumor suppressors.[1,26] Inflammatory cells, including macrophages and lymphocytes, accumulate in the stromal tissues surrounding thyroid cancers.[26] In addition to inflammation localized within the thyroid gland, systemic inflammation may play a role in the development and/or progression of thyroid cancer.[26] Multiple cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-6, IL-1β, IL-10, and transforming growth factor (TGF)-β, have been investigated as potential mediators of this process.[1–3] Hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1), stemming from insulin resistance, are alternative hypotheses proposed for the development of thyroid cancer.[1,26] Following binding to the insulin receptor, insulin triggers downstream signaling pathways, including the AKT/mTOR/PI3K and ERK/RAS/MAPK pathways, which play critical roles in cancer cell proliferation and survival.[26]

The surplus adiposity itself, even without metabolic deterioration, may influence the development of thyroid cancer. Adipose tissue is an active endocrine organ that secretes various adipokines. The expansion of adipose tissue in obesity may contribute to cancer development through the dysregulated secretion of adipokines.[9,12,26] Adiponectin, an adipokine, exerts antitumor effects by activating the AMP-activated protein kinase pathway in addition to enhancing insulin sensitivity and reducing inflammation.[27,28] Reduced adiponectin levels in obesity have been identified as an independent risk factor for obesity-related cancer.[2,3,26] Conversely, leptin has been demonstrated to stimulate cell proliferation, suppress apoptosis, and promote the migratory activity of thyroid cell lines by activating the PI3K/Akt signaling pathway.[26] Given the increased expression of leptin and its receptors in thyroid cancer cells, the autocrine/paracrine effect of leptin is a plausible mechanism.[29,30] Leptin might exert a direct influence on cancer initiation or tumor progression independent of systemic effects.[29,30] Elevated serum TSH levels could potentially stimulate the proliferation and growth of thyroid cells, promote mutation rates, and contribute to the development of thyroid cancer.[31] The increase in intracellular cAMP levels mediated by the TSH receptor is regarded as a significant stimulus for thyroid cell proliferation. This mechanism interacts with various growth factors, such as insulin, IGF-1, and other pathways including the RAS-BRAF and PI3K/AKT pathways.[32] Circulating estradiol presents a potential mechanism for thyroid carcinogenesis, as adipocytes produce estrogen through aromatase activity, and obesity is correlated with elevated levels of estradiol.[33] Estrogen is a potent growth factor for malignant thyroid cells.[34] Estrogen exerts its growth-promoting effect through both classical genomic and non-genomic pathways, which are mediated via a membrane-bound estrogen receptor.[34] This receptor is connected to the tyrosine kinase signaling pathways MAPK and PI3K.[34]

However, the relationship between MHO and thyroid cancer remains controversial. A substantial cohort study involving 255,051 participants in Korea revealed that women classified as MUO, but not MHO, exhibited an elevated risk of thyroid cancer.[9] There is a suggestion that hormones may contribute to maintaining a healthy status in certain individuals with obesity. Factors such as geographical location, metabolic activity, and histological characteristics may partially determine metabolic health.[35] Despite accumulating high levels of body fat, MHO individuals exhibit heightened insulin sensitivity and lower levels of C-reactive protein along with elevated concentrations of adiponectin 36. Additional evidence indicates that MHO individuals are more physically fit than their metabolically unhealthy counterparts.[37] This advantageous profile could potentially lower the susceptibility to specific types of cancers associated with obesity, such as liver and bladder cancers. Numerous studies have indicated that a subset of individuals with obesity might experience protection from metabolic complications associated with obesity or could face a significantly lower risk than anticipated considering their level of obesity.[12]

This systematic review represents the first comprehensive exploration of the association between metabolic obesity phenotypes and thyroid cancer risk. Thorough adherence to PRISMA guidelines ensured a rigorous approach, including a comprehensive literature search across multiple databases and detailed data extraction. Mechanistic insights enrich the interpretation of findings. However, limitations include the limited number of included studies and their heterogeneity, which may affect generalizability. The absence of meta-analysis and potential biases such as publication bias are acknowledged. Further research addressing these limitations is needed to strengthen the evidence base and inform clinical practice.

5 | CONCLUSION

In summary, this review outlines the intricate link between metabolic obesity types and thyroid cancer risk, drawing insights from limited but informative studies. It suggested that obesity, especially with

metabolic issues, increases thyroid cancer risk, with variations between genders. Central fat distribution is a significant predictor alongside BMI. Mechanistically, inflammation, altered hormone levels, and disrupted signaling pathways likely contribute to thyroid cancer development. However, controversies exist regarding the risk of metabolically healthy obesity, possibly due to protective metabolic profiles. These findings emphasized the importance of assessing metabolic obesity types in thyroid cancer prevention, though further research is needed for better understanding and intervention strategies.

AUTHOR CONTRIBUTIONS

Behnaz Abiri and Mehdi Hedayati conceived and designed the study. Behnaz Abiri and Majid Valizadeh conducted the systematic search, screened articles, and read the full texts for eligibility. Behnaz Abiri and Majid Valizadeh extracted data from the original studies. Behnaz Abiri, Mehdi Hedayati and Majid Valizadeh contributed to the interpretation of the results and wrote the first draft of the manuscript. Mehdi Hedayati, and Majid Valizadeh critically revised the manuscript. All authors have read and approved the final manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, BA.

CONSENT FOR PUBLICATION

All authors have given consent for the paper to be published by the corresponding author.

ORCID

Majid Valizadeh https://orcid.org/0000-0002-3155-1951

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