PIĄTKOWSKA, Karolina, JAROŃ, Aleksandra, WIKLIŃSKA, Agata, ŚLIWIŃSKA, Martyna, WÓJTOWICZ, Katarzyna, WALCZAK, Agata, NIEGOWSKA, Wiktoria, WIRKIJOWSKI, Jakub, GAJEK-FLANCZEWSKA, Wiktoria, FLANCZEWSKI, Sebastian, WOŹNIAK, Paulina and KIDACKI, Kajetan. Obesity and the Risk of Thyroid Cancer: A Literature Review. Quality in Sport. 2024;19:54187. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.54187
https://apcz.umk.pl/QS/article/view/54187

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 09.08.2024. Revised: 19.08.2024. Accepted: 29.08.2024. Published: 01.09.2024.

Obesity and the Risk of Thyroid Cancer: A Literature Review

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ABSTRACT

Introduction and aim of the study: Thyroid cancer is considered the most common endocrine malignant worldwide in recent years. Also, obesity has become a true pandemic. The correlation between the increase in cases of not only obesity but also thyroid cancer could not be explained solely by earlier and more meticulous cancer diagnoses. This study aims to review the literature on the relationship between obesity and the risk of thyroid cancer.

Materials and Methods: The authors conducted a comprehensive review of the literature available in PubMed and Medline databases focusing on the terms "thyroid cancer" and "obesity".

Results: Obesity is associated with a state of chronic inflammation and nonspecific activation of the immune system, leading to the production of cytokines and adipokines. These elements, through complex mechanisms, directly and indirectly promote carcinogenesis. Despite the association of excessive body weight with malignant tumor development, oncological treatment cannot rely solely on lifestyle changes and should be conducted precisely as it is for individuals with normal body weight. Another popular research topic in recent years has been circadian rhythm disorders. These disorders are confirmed to be a pro-carcinogenic factor but are also considered as an element that could accelerate diagnosis.

Conclusions: Understanding the relationship between obesity and thyroid cancer, primarily molecular mechanisms is essential for developing effective preventive and therapeutic strategies to reduce the risk of thyroid cancer in obese patients.
KEY WORDS: thyroid carcinoma, obesity, overweight, risk factors

INTRODUCTION

Thyroid cancer is currently the most common malignant tumor of the endocrine system. [1] It accounts for approximately 1% of all malignant tumors (0.5% in men and 2.6% in women), and its incidence has significantly increased in recent years. [2], [3] The rapid rise, particularly in the early stages of thyroid cancer, can be linked to increased medical surveillance and the widespread use of imaging diagnostic techniques. However, the incidence of larger and more aggressive subtypes of thyroid cancer has also increased over time, suggesting a potential role for environmental or lifestyle-related risk factors, especially as the prevalence of overweight and obesity has risen globally. [4], [5]

Thyroid cancer (TC) originates from follicular epithelial cells or parafollicular C cells and is classified into three main histological types: differentiated (papillary and follicular TC), undifferentiated (poorly differentiated and anaplastic TC), and medullary TC, which arises from parafollicular C cells. (Figure.1) [6] Papillary thyroid cancer is the most common type with the best overall prognosis. [7] Thyroid cancer occurs about three times more frequently in women than in men, similar to almost all thyroid diseases. [8] However, men are more likely to die from this cancer than women. The average age at which thyroid cancer is diagnosed is 51 years. [8] Only about 20% of cases occur in individuals under the age of 30. [2] Risk factors include exposure to ionizing radiation, especially during childhood, a family history of thyroid cancer, including familial medullary cancer, certain genetic syndromes such as Cowden syndrome, Carney complex, and MEN2 syndrome. Iodine deficiency and related endemic goiter are associated with an increased incidence of follicular cancer. On the other hand, a diet high in iodine may increase the risk of papillary thyroid cancer. According to the International Agency for Research on Cancer (IARC), overweight or obese individuals are at a higher risk of developing thyroid cancer than those without overweight, and the risk appears to increase with a higher body mass index (BMI), making excess body weight another risk factor. [8]

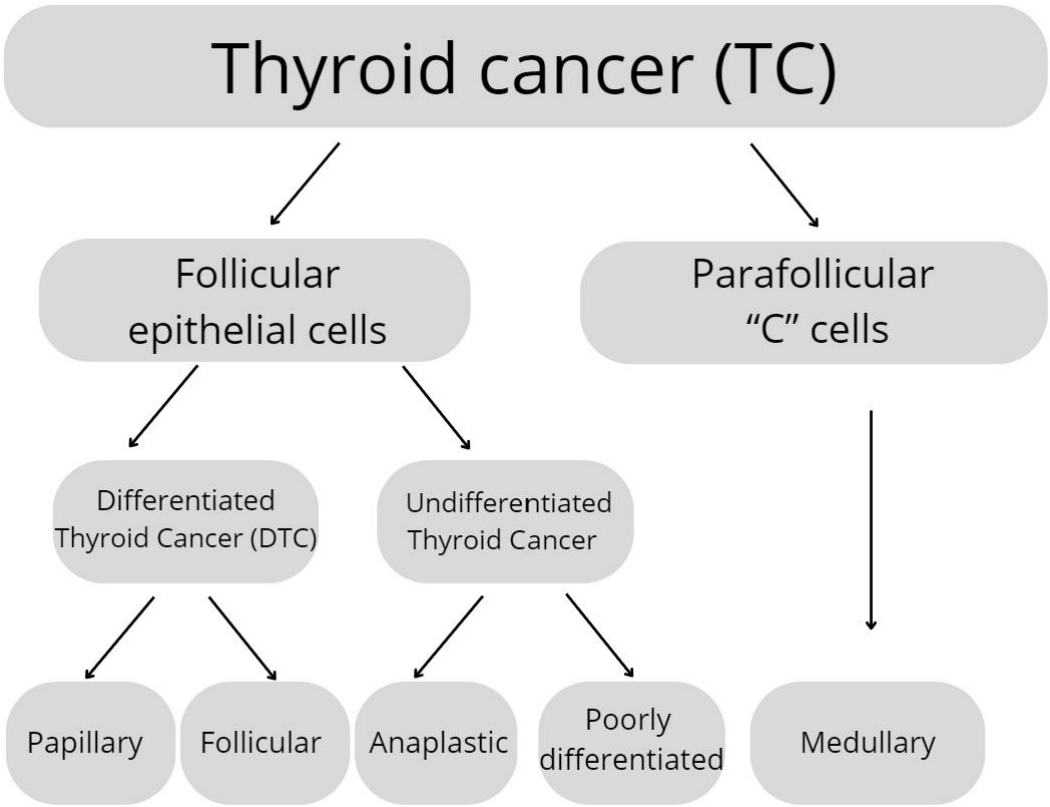

Figure 1. Types of thyroid cancer.

Five-year relative survival rates depend on the type of cancer. The average 5-year survival rate is over 90% for women and about 80% for men. [2] The lowest survival rate is observed in anaplastic cancer, ranging from 4 to 40% depending on the stage of the tumor. [8] Symptoms of thyroid cancer can be ambiguous and often include a growing neck nodule, enlargement of cervical lymph nodes, difficulty swallowing, hoarseness, shortness of breath, neck or throat pain. Treatment for thyroid cancer depends on the type of tumor, the stage of the disease, and the patient's overall health. The main treatment methods include surgery, most often total thyroidectomy, radiotherapy, especially in advanced cancer cases. Additionally, radioactive iodine treatment is mainly used for papillary and follicular cancer, as well as targeted therapies and immunotherapies in advanced cases of medullary and anaplastic cancer. [2], [6]

This study aims to review the literature on the relationship between obesity and the risk of thyroid cancer. Two databases were searched: PubMed and Medline, using the terms "thyroid cancer" and "obesity". Publications concerning the correlation between body mass index (BMI) and the risk of thyroid cancer, as well as the impact of obesity on thyroid function at

the cellular and molecular levels, were analyzed. The aim is also to emphasize the need for further research in this field and to highlight the importance of an interdisciplinary approach in the treatment and prevention of thyroid cancer in the context of the growing obesity epidemic.

CELLULAR AND MOLECULAR MECHANISMS UNDERLYING THE LINK BETWEEN OBESITY AND THYROID CANCER DEVELOPMENT

The incidence of thyroid cancer is rising, partially due to more sensitive diagnostic procedures, but also influenced by various environmental factors, including obesity. Obesity is associated with the development and progression of many cancers and is considered the second most common, preventable, and modifiable cause of cancer development after smoking. [9] However, little is known about the underlying causal mechanisms linking obesity and thyroid cancer. Metabolic disorders related to obesity, such as type 2 diabetes, metabolic syndrome, and hypothyroidism, have been found to be associated with thyroid cancer risk, although evidence is limited. [4], [10], [11] These conditions are characterized by metabolic disturbances, including hyperinsulinemia and inflammation. These states play a role in the pathophysiology of obesity-induced thyroid cancer.

Numerous studies have investigated the relationship between obesity and the risk of thyroid cancer. The molecular mechanisms underlying the association between TC development and obesity include chronic inflammation, oxidative stress, adipokines, insulin-like growth factors, hyperinsulinemia and insulin resistance, and estrogens.[12] However, these mechanisms are complex and not fully understood. [Figure 1.]

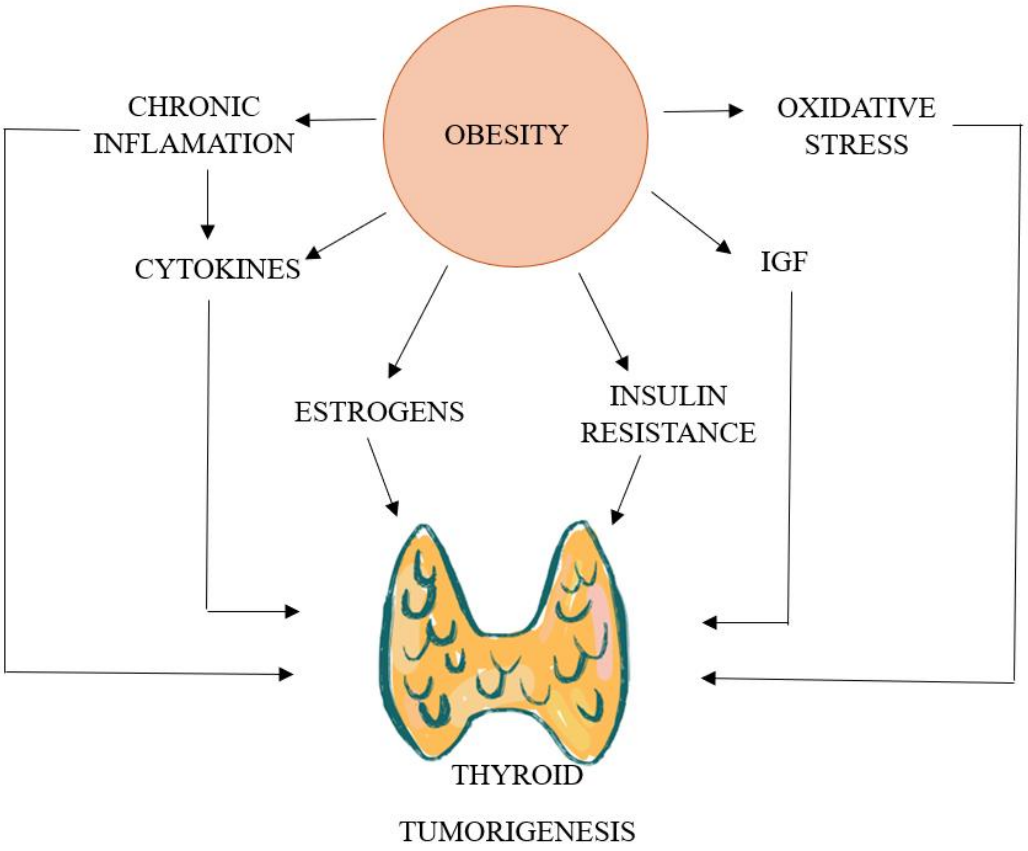

Figure 2. Molecular Mechanisms Underlying the Link Between Thyroid Cancer (TC) Development and Obesity [12]

Chronic Inflammation

Obesity is accompanied by chronic inflammation, characterized by elevated systemic inflammatory markers and immune system activation. [13] Chronic inflammation causes an increase in the expression of inflammatory cytokines. Additionally, in obesity, the hypertrophy of adipocyte cells promotes the production of pro-inflammatory factors. High concentrations of adipocytokines promoted by obesity can impair cell proliferation and promote tumorigenesis in the thyroid. Adipocytokines include adiponectin (APN), leptin, resistin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). [14] In chronic inflammation, there is an increased production of leptin, which is pro-inflammatory, pro-angiogenic, and proliferative. [15] In patients with thyroid cancer (TC), a correlation has been observed with elevated levels of circulating leptin, which supports neovascularization in tumor tissue and induces VEGF expression. [16] Additionally, there is a decrease in adiponectin, which is anti-inflammatory, anti-angiogenic, and anti-proliferative, leading to increased cell proliferation and survival and enhanced angiogenesis. [15]

In obese individuals, increased levels of cytokines IL-6 and TNF-α are often observed, which have also been noted in thyroid cancer, and may contribute to TC development. [17] IL-6 supports the growth and proliferation of anaplastic thyroid cancer stem cells and enhances the epithelial-mesenchymal transition (EMT), contributing to the spread of thyroid cancer metastases. TNF-α is a pro-inflammatory factor involved in tumor cytotoxicity and angiogenesis.[18]

Metabolic Disturbances

Obesity is associated with a state of chronic inflammation, which is linked to the development of hyperglycemia, vascular damage, hyperlipidemia, insulin resistance, and hyperinsulinemia. All these conditions are associated with increased oxidative stress, which contributes to the development and progression of various cancers. In thyroid cancer, excessive production of reactive oxygen species and lower activity of antioxidant systems have also been described. [19], [20], [21]

Insulin Resistance and Hyperinsulinemia

Obesity is a well-known risk factor for hyperinsulinemia and insulin resistance (IR), and IR is associated with an increased risk of thyroid cancer. [22] Moreover, insulin resistance was found to be more common in TC patients with BMI >25 compared to control subjects with the same BMI. [23]Similar results were reported in a recent meta-analysis indicating a higher risk of TC in patients with IR, diabetes, high BMI, and hypertension. In thyroid cancer patients, higher expression of insulin-like growth factor receptors (IGF-1R) has also been described. Obesity leads to increased levels of IGF, which have the ability to promote cancer cell growth and survival. [24] Many studies have shown overexpression of IGF ligands and receptors in various cancers, including thyroid cancer. [25], [26] This overexpression is associated with cellular transformation, proliferation, and suppression of apoptosis, resulting in poor prognosis. Additionally, IGF-binding proteins may have suppressive effects on thyroid cancer. [27]

Estrogens

Both obesity and thyroid cancer are more common in women than in men, suggesting a link with levels of endogenous estrogens. In obese individuals, elevated levels of estrogens are observed, which may influence the development of cancer cells in the thyroid. [28] Estrogens act through genomic and non-genomic pathways mediated by nuclear estrogen receptors (ER), which exist in two different isoforms: ER-α and ER-β. The effect of estrogen on thyroid cancer cell growth depends on the balance between the expression of ER-α and ER-β in the tumor. Overexpression of ER-α has been reported in female thyroid cancer patients, especially

postmenopausal women. Additionally, estrogens increase angiogenesis in thyroid cancer by regulating VEGF secretion from thyroid cells.[29], [30]

Understanding these molecular mechanisms is essential for developing effective preventive and therapeutic strategies to reduce the risk of thyroid cancer in obese patients.

CONNECTION BETWEEN OBESITY AND THYROID CANCER

Obesity has become a global epidemic in recent years. An estimated 38% of the world's adult population will be overweight, and another 20% will be obese.[31]

The association between excess body weight and increasing risk for cancer is convinced for at least 13 anatomic sites. [32] Moreover, obesity is the second most common, preventable, and modifiable cause of carcinogenesis, after smoking. [33]

The incidence of obesity-related thyroid carcinoma (TC) has increased rapidly in the past few decades. [34] The simultaneous increase in both thyroid cancer and obesity has led to studies investigating the correlation between the two. [35] It cannot be entirely explained by early and meticulous diagnosis. [36] In the case of thyroid cancer (TC), obesity is a confirmed risk factor. [37], [38] Additionally, patients who were overweight and obese had a significantly greater risk of having a tumor larger than 1 cm and multifocal nodules compared to normal weight patients [39]

A positive correlation has been observed between BMI and the incidence of papillary, follicular, and anaplastic thyroid carcinomas, but not medullary, thyroid carcinomas. [40]

In a study of Caucasian subjects, there were not demonstrate any association between BMI and aggressiveness of differentiated thyroid cancer (DTC). [41]

The probable mechanism linking obesity with the development of cancer is complex. It involves multiple factors both at the systemic and cellular level. [39] Recent data have underlined the contribution of the triad of overweight/obesity, IR, and adipocytokines in cancer. [32] Another study underlines the impact of disruptions in insulin metabolism, adipokines, inflammation, and sex hormones [39]

CONNECTION BETWEEN CIRCADIAN RHYTHM DISRUPTION AND CANCER

Increasingly, alongside obesity, attention is being drawn to another contemporary issue. Disruption of circadian rhythm is a potential factor in thyroid tumorigenesis. [42] [43] . A study from 2013 proposed an association between insomnia and a higher incidence of TC in post-menopausal non-obese women. [44]

It has been observed that exposure to light at night lowers melatonin levels (responsible for the proper functioning of the circadian rhythm) and increases TSH plasma levels. [42]

A recent study from the United States supports the hypothesis of a positive correlation between increased light exposure and a higher risk of developing thyroid cancer (especially papillary thyroid carcinoma and anaplastic thyroid carcinoma). [45]

At the genomic level, in the case of papillary carcinoma, an increased amount of tissue inhibitor of metalloproteinases 1 has been observed. It has also been noted that transformation into benign nodular thyroid tissue does not alter the function of the circadian oscillator, whereas malignant transformation does cause such a change. Additionally, the dysregulation of various clock genes including CRYs, PER1-2-3, REV-ERBs, and ROR α-β-γ is associated with a higher risk of developing thyroid cancer. [42] These findings require further research as they may provide new therapeutic options.

Currently, studies are being conducted on the use of chronotherapy in cancer treatment. Chronotherapy could support cancer treatment in three areas:

1. Supporting an ideal circadian rhythm.
2. Optimizing chemotherapy and radiotherapy by maximizing their therapeutic effects (selecting the perfect time for dosing, which can reduce adverse effects).
3. Because almost all tumors have disruptions in the expression of clock genes, we can use small molecules that alter circadian clock genes.. [42], [46]

These are promising methods that could support the treatment of various cancers. Additionally, circadian rhythm disruptions may be a potential risk factor that could play a role in the changing epidemiology of thyroid cancers. [43]. Understanding these disorders may improve the preoperative diagnosis of thyroid cancers. [47]

It is also worth mentioning that there are many studies linking the aforementioned disorders. According to these studies, circadian rhythm disorders have long-term health consequences and become a risk factor for obesity and hormone-dependent cancers.. [43], [47], [48], [49], [50] (Figure 3.)

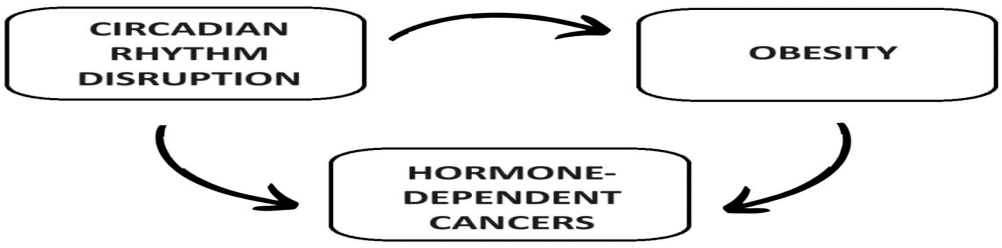

Figure 3. The relationship between circadian rhythm, obesity, and thyroid cancer.

TREATMENT OF OBESITY AND CANCER

Adipose tissue is an endocrinologically active organ that, through the production of adipokines, hormones, and growth factors, disrupts normal cell proliferation, leading to tumor formation. [35] In cancer prevention, it generally seems more important to prevent weight gain than to lose weight. [32] In the case of bariatric surgery based on one Swedish intervention trial, this surgical procedure has been shown more effective at lowering cancer risk in women compared to men.[51] Continuing this, some studies have shown that bariatric surgery for weight loss is associated with a lower risk of obesity-related cancers and all types of cancer. Additionally, cancer mortality was significantly lower in women after bariatric surgery compared to the non-surgical group. [52]

However, in the case of thyroid cancer, this correlation is not justified, for example, in Wilson's 2023 study, on the contrary, no significant reduction in the incidence of thyroid cancer was found after bariatric surgery compared to patients with morbid obesity who did not undergo bariatric surgery. [53]

PROGNOSIS

The topic of prognosis and aggressiveness of thyroid cancer in individuals with or without obesity remains a subject of debate. It is a complex issue because various confounding factors, such as gender, age, smoking, and other variables, influence the final outcome.

A 2020 study demonstrates that an increase in BMI is associated with greater aggressiveness of papillary thyroid carcinoma (PTC) and also observed gender differences – the rates of obesity and aggressiveness were significantly higher in men. [54]

Studies by Kim confirm a positive correlation between obesity and a higher incidence of macro-PTC (>1cm), increased frequency of extrathyroidal extension, vascular invasion, and intermediate-risk tumors. This correlation was observed in women but not in men. [55]

According to research conducted by Zhao, patients with higher BMI had larger and multifocal thyroid cancers (PTC). [39]

A Polish study did not identify BMI as a risk factor for the aggressiveness of DTC (differentiated thyroid carcinoma). Furthermore, after the observation period, no association was found between BMI and response to treatment or overall survival. [56]The available studies on the impact of obesity on the aggressiveness of TC (thyroid cancer) remain inconclusive. Therefore, attention should be focused on the early detection of cancers, and treatment in obese Patients should be conducted conventionally, just as in Patients with normal body weight. [57]

OBESITY PARADOX

There is also a phenomenon described as the "obesity paradox," which refers to the paradoxical protective effect between body mass index (BMI) and clinical outcomes. [58] This phenomenon is more frequently analyzed in cases of renal, cardiovascular, pulmonary, and metabolic disorders, as well as sepsis, and is less commonly associated with cancer. Nevertheless, recent epidemiological data suggests that obesity may be a protective factor for certain types of cancer and may decrease mortality rates [32], [59]More, Trestini's study suggests that patients with a normal body mass index (BMI) have worse outcomes than obese patients. [60]

Some explanations for this phenomenon are based on methodological limitations, such as the use of BMI as a measure of general adiposity, the inadequacy of BMI as a measure of body fatness in oncology patients who often experience changes in body weight and composition, or confounders such as age, smoking, physical activity, etc. [32], [59]

ADOLESCENT OVERWEIGHT AND OBESITY AND THE RISK OF THYROID CANCER IN ADULTHOOD

Most studies assess the relationship between adult obesity and the risk of thyroid cancer in this patient group. However, Kyoung-Nam Kim focuses on the association between obesity and overweight in adolescents and the risk of thyroid cancer, particularly papillary thyroid

cancer. The prevalence of overweight and obesity has increased in recent years among adolescents as well. It has been found that a BMI ≥ 25.0 in adolescents is associated with a higher risk of papillary thyroid cancer in adulthood compared to a BMI < 23.0. This association proved to be stronger in males and individuals with a current BMI ≥ 25 compared to females and individuals with a current BMI < 25. Additionally, overweight and obesity in adolescents diagnosed with papillary thyroid cancer were associated with extrathyroidal tumor spread and larger tumor size. The results also suggest that overweight and obesity in adolescents may increase the risk of thyroid cancer in adulthood, even if individuals are no longer overweight or obese when they reach adulthood. However, the point estimate of the relationship between BMI and the risk of thyroid cancer was significantly lower among individuals with a current BMI < 25.0 than those with a BMI ≥ 25.0. This suggests that the risk of thyroid cancer can be reduced by controlling body weight in adulthood, even among individuals who were overweight or obese during adolescence, although it remains higher than among those who had a normal weight during adolescence. [61] Another Korean study, on the other hand, draws attention to the increase in thyroid cancer incidence in children, suggesting a significant association with the higher prevalence of obesity in this patient group. [62]

CONCLUSIONS:

The relationship between obesity and thyroid cancer is multifaceted, involving complex interactions at both the systemic and cellular levels. The increasing prevalence of obesity globally corresponds with a rising incidence of thyroid cancer, suggesting a significant link between the two. Metabolic disturbances commonly associated with obesity, such as insulin resistance, hyperinsulinemia, and chronic inflammation, play crucial roles in promoting thyroid carcinogenesis. Elevated levels of adipokines and estrogens further contribute to this risk, highlighting the intricate mechanisms through which obesity influences thyroid cancer development.

Disruptions in circadian rhythms, another emerging risk factor, may also contribute to the rising incidence of thyroid cancer. The concept of chronotherapy, which optimizes treatment timing to align with the body's biological clock, offers a promising avenue for improving therapeutic outcomes in thyroid cancer patients.

Promoting a healthy lifestyle, including a healthy diet and regular physical activity, can help reduce obesity and thus reduce the risk of thyroid cancer. Public health campaigns should take into account these relationships to more effectively combat both obesity and cancer.

Given the complexity of interactions, further research is essential to elucidate the underlying mechanisms linking obesity and thyroid cancer. An interdisciplinary approach that integrates insights from endocrinology, oncology, and chronobiology is crucial for developing effective prevention and treatment strategies. Addressing the obesity epidemic through public health initiatives and personalized medical interventions will be vital in mitigating the rising burden of thyroid cancer and improving patient outcomes.

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Acknowledgments: Not applicable.

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