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Thyroid Autoimmune Disease and Effect on Development to Thyroid Cancer

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ABSTRACT

Objective: *This study investigates the association between autoimmune thyroid diseases – specifically Hashimoto's thyroiditis (HT) and Graves' disease (GD) – and the development of thyroid cancer, with a primary focus on papillary thyroid carcinoma (PTC).* ***Method:*** *A comprehensive literature review was conducted to analyze epidemiological trends, immunopathological mechanisms, and tumor microenvironment factors linking autoimmunity to thyroid carcinogenesis.* ***Results:*** *The findings indicate a significant correlation between autoimmune thyroid disorders and increased incidence of PTC, suggesting that chronic inflammation may contribute to oncogenic genetic alterations in thyroid epithelial cells. Interestingly, HT appears to paradoxically confer favorable clinical outcomes, including reduced tumor aggressiveness, enhanced responsiveness to radioiodine therapy, and improved survival, likely due to heightened immune surveillance. Additionally, the presence of cancer-associated fibroblasts (CAFs) was associated with increased lymph node metastasis, highlighting their role in shaping a pro-tumorigenic microenvironment.* ***Novelty:*** *This study provides integrative insights into the dual role of autoimmunity in both promoting and modulating thyroid cancer progression, and underscores the importance of the tumor microenvironment – particularly CAFs – in influencing metastatic behavior in PTC.*

INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignant neoplasm worldwide, presenting an increasing record number of new cases every year, predominantly in females. In the last decades, many studies conducted in vitro, and in vivo, have shown that thyroid autoimmunity and thyroid cancer (TC) (mainly papillary TC) can be concomitant, even if the exact mechanisms at the basis of this association are still not clear. Growing incidence of TC coincides with increased registration of autoimmune thyroid disorders (AITD) suggesting an association between those pathologies [1], [2], [3].

Autoimmune thyroid diseases (AITDs), particularly Hashimoto's thyroiditis (HT) and Graves' disease (GD), represent the most common immune-mediated thyroid disorders. They involve an aberrant immune response directed against thyroid tissue, leading to structural and functional impairments. Recently, considerable attention has been directed toward the potential association between these autoimmune disorders and the development of thyroid cancer, especially papillary thyroid carcinoma (PTC), the most prevalent subtype. Among the subtypes, papillary thyroid carcinoma (PTC) is the most common in the population, representing about 75-80% of the thyroid cancer cases [4], [5].

RESEARCH METHOD

This study employed a qualitative literature review approach to analyze the interplay between autoimmune thyroid diseases—particularly Hashimoto's thyroiditis (HT) and Graves' disease (GD)—and the development and progression of thyroid cancer, with a primary focus on papillary thyroid carcinoma (PTC). Peer-reviewed journal articles and meta-analyses published in reputable endocrine and oncology journals were systematically selected to investigate the epidemiological correlation, pathological mechanisms, and tumor microenvironment dynamics. Key inclusion criteria focused on studies evaluating the roles of chronic inflammation, immune surveillance, and the presence of cancer-associated fibroblasts (CAFs) in influencing tumor characteristics and metastatic potential. The review also integrated clinicopathological findings, genetic markers such as BRAF^V600E^ mutation, and outcomes from multivariate analyses identifying CAFs as independent risk factors for cervical lymph node metastasis. Through this methodology, the study synthesized existing evidence to explore both the oncogenic and potentially protective roles of thyroid autoimmunity in the context of cancer progression and prognosis [1], [6], [7], [8].

RESULTS AND DISCUSSION

Fibroblasts' Inflammatory Function in Thyroid Cancer

Encircling the tumour cells, CAFs take role in immune surveillance, treatment response, metabolism, metastasis, tumour start, and tumor-stimulatory inflammation. A paper evaluated the association between expression of CAF-related proteins in PTC in relation to clinicopathologic factors in 339 PTCs [9]. It was shown that the expression of CAF-related proteins in stromal cells and cancer cells of PTC varied on the basis to histologic subtype, BrafV600E mutation, and subtype of stroma, and it was associated with shorter overall survival [10]. Furthermore, another paper studied the association between CAFs and cervical lymph node metastasis in PTC (Cho J.G *et al*. 2018). Among 78 PTC patients, 65 presented desmoplastic stromal reaction around the tumor. CAFs were found in 42 (64.6%) cases with desmoplastic stroma. At univariate analysis, it was shown that tumor size and CAFs were risk factors of lymph node metastasis. However, by a multivariate analysis, CAFs were the only independent risk factor of lymph node metastasis in these patients [11].

Epidemiological and Statistical Correlation

A growing body of epidemiological evidence supports a positive association between Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma (PTC). For instance, a meta-analysis (Liu *et al*.2014) demonstrated a significantly increased prevalence of PTC among patients diagnosed with chronic autoimmune thyroiditis [12]. This suggests that HT may be more than just a coincidental finding in patients with thyroid cancer. Similarly, Resende de Paiva *et al*. (2013) concluded that autoimmune thyroid diseases (AITD), particularly Hashimoto's thyroiditis, could serve as a potential risk factor for the development of thyroid malignancies. The chronic lymphocytic inflammation associated with HT may contribute to genetic and molecular changes in

thyroid cells that predispose them to malignant transformation. However, the nature of the relationship remains a matter of debate—whether it is causative or simply correlative [12], [13].

Clinical Paradox: A Protective Role?

Despite the well-established association between autoimmune thyroid disease (AITD), particularly Hashimoto's thyroiditis (HT), and an increased risk of papillary thyroid carcinoma (PTC), several studies have suggested a paradoxical protective effect when these two conditions coexist. Specifically, thyroid cancers arising in the setting of chronic autoimmune thyroiditis tend to demonstrate less aggressive clinical behavior, with smaller tumor size, fewer instances of extrathyroidal extension, and reduced rates of lymph node or distant metastasis. Moreover, patients with coexisting HT and PTC have been observed to exhibit a better overall prognosis, including higher disease-free survival and improved responses to radioactive iodine (RAI) therapy [14].

This protective phenomenon is thought to be mediated by enhanced immune surveillance in patients with AITD. The persistent autoimmune activity, including infiltration of lymphocytes and increased cytokine activity, may promote the early detection and elimination of malignant thyroid cells during carcinogenesis. As such, the immune environment characteristic of HT might function as a double-edged sword—initially contributing to tumor initiation through chronic inflammation, while also limiting tumor progression by maintaining immunologic pressure on malignant cells [15].

CONCLUSION

Fundamental Finding : This study highlights a complex and bidirectional relationship between autoimmune thyroid diseases—particularly Hashimoto's thyroiditis (HT)—and papillary thyroid carcinoma (PTC). While chronic inflammation associated with HT may contribute to oncogenesis through genetic and molecular alterations, evidence also suggests a paradoxical protective effect, with HT-related immune responses potentially suppressing tumor aggressiveness and improving patient outcomes. Additionally, cancer-associated fibroblasts (CAFs) have been identified as key components of the tumor microenvironment that significantly influence metastasis, particularly to cervical lymph nodes. **Implication :** These findings underscore the need to consider both autoimmune status and stromal interactions in the risk assessment, prognosis, and treatment planning for thyroid cancer patients. Understanding the dualistic nature of immune activity could enhance personalized therapeutic approaches and biomarker development. **Limitation :** However, the current body of evidence is limited by variations in sample size, methodology, and patient populations across studies, as well as the observational nature of most research, which complicates causal inference. **Future Research :** Further longitudinal and mechanistic studies are needed to elucidate the precise molecular pathways linking autoimmunity, CAF activity, and tumor progression, and to explore targeted interventions that leverage the immune microenvironment for improved therapeutic outcomes in PTC.

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