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INVESTIGATING THE ASSOCIATION BETWEEN HYPOTHYROIDISM AND BREAST CANCER PROGNOSIS IN WOMEN UNDERGOING ENDOCRINE THERAPY: A NARRATIVE REVIEW

Narrative Review

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ABSTRACT

Background: Hypothyroidism is a prevalent endocrine disorder that may affect treatment outcomes in breast cancer patients, particularly those receiving endocrine therapy. As both conditions commonly coexist in women and share hormonal pathways, understanding their interaction is increasingly relevant to clinical decision-making and survivorship care.

Objective: This narrative review aims to explore the influence of hypothyroidism on prognosis, recurrence, and therapeutic outcomes in women undergoing endocrine therapy for breast cancer.

Main Discussion Points: The review synthesizes recent evidence across several key themes: the impact of radiation-induced hypothyroidism, the biological role of thyroid hormones in breast cancer progression, and the potential influence of thyroid hormone replacement—particularly levothyroxine—on endocrine therapy efficacy. It also addresses the limitations of current studies, including methodological inconsistencies, limited prospective data, and poor generalizability. Mechanistic insights suggest a complex interaction between thyroid and estrogen receptor signaling, which may influence tumor behavior and treatment response.

Conclusion: While evidence supports routine thyroid monitoring and consideration of thyroid-sparing techniques in radiotherapy, conclusive data on the prognostic significance of hypothyroidism remain limited. Future prospective trials and mechanistic studies are essential to inform clinical guidelines and optimize personalized care.

Keywords: Breast Cancer, Hypothyroidism, Endocrine Therapy, Radiation Toxicity, Thyroid Hormone Replacement, Narrative Review.

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INTRODUCTION

Breast cancer remains one of the most prevalent malignancies affecting women worldwide, with over two million new cases and approximately 685,000 deaths reported in 2020 alone, according to GLOBOCAN statistics. Despite advancements in early detection and multimodal treatment, including surgery, chemotherapy, radiation, and endocrine therapy, mortality and recurrence rates remain a significant public health concern. Endocrine therapy, such as tamoxifen and aromatase inhibitors, is a cornerstone of treatment in hormone receptor-positive breast cancer, effectively improving disease-free and overall survival. However, the interplay between comorbid endocrine conditions—particularly hypothyroidism—and breast cancer prognosis is an emerging area of interest, given the common endocrine axis shared between thyroid and reproductive hormones.

Hypothyroidism, characterized by insufficient thyroid hormone production, is a common endocrine disorder with a global prevalence estimated between 4% and 10%, increasing with age and more frequent among women. It may occur spontaneously, as an autoimmune phenomenon, or iatrogenically after radiotherapy or systemic therapies in breast cancer patients. Thyroid hormones play an essential role in regulating cellular metabolism, proliferation, and differentiation, and their deficiency may influence cancer pathophysiology and treatment response. Notably, triiodothyronine (T3) and thyroxine (T4) can exhibit estrogen-like activity on breast cancer cells, potentially modulating tumor growth, progression, and response to endocrine therapy (1).

Research exploring the association between thyroid dysfunction and breast cancer has yielded conflicting results. Some studies suggest a protective effect of hypothyroidism against breast cancer development and progression. For instance, a large cohort study of postmenopausal women found that hypothyroidism, especially when treated with levothyroxine, was associated with a decreased risk of invasive breast cancer (2). Similarly, a population-based Danish study observed no association between hypothyroidism and breast cancer recurrence or overall mortality, suggesting that thyroid dysfunction does not significantly alter the clinical course of breast cancer (3). Moreover, findings from a UK population-based study reported no significant link between hypothyroidism—diagnosed before or after cancer onset—and cancer-specific or all-cause mortality in breast cancer patients (4).

Conversely, other investigations highlight nuanced effects, including potential interactions with hormonal therapies. A recent study demonstrated that thyroid hormone replacement therapy (THRT) in patients with estrogen receptor-positive breast cancer was associated with worse disease-free and disease-specific survival, possibly due to synergistic activation of estrogen and thyroid hormone receptors that promote oncogenic pathways (5). Experimental studies further support this by showing that thyroid hormones can enhance cell proliferation in hormone-responsive breast cancer models, particularly when combined with estradiol (6). This raises concerns regarding the indiscriminate use of THRT in women undergoing endocrine therapy, as thyroid hormones may attenuate or antagonize the benefits of estrogen suppression.

Adding to the complexity, some studies refute a significant relationship altogether. A case–control study using the Disease Analyzer database concluded there was no meaningful association between hypothyroidism and breast cancer risk (7). Others, such as the UK Biobank cohort analysis, found that while hypothyroidism was not associated with increased risk overall, a modest reduction in breast cancer risk was noted more than ten years after hypothyroidism diagnosis (8). These discrepancies may stem from methodological variations, including differences in population demographics, thyroid disease definitions, treatment modalities, and follow-up durations.

Given the clinical and biological plausibility, the influence of hypothyroidism on breast cancer outcomes, particularly in the context of hormonal therapy, warrants comprehensive evaluation. This is especially relevant considering the high co-occurrence of these conditions in aging female populations and the increasing survivorship in breast cancer. While endocrine therapy remains effective, coexisting hypothyroidism may either potentiate or hinder therapeutic efficacy, depending on the timing of onset, treatment status, and hormone receptor profile of the tumor.

The objective of this narrative review is to synthesize current evidence on the association between hypothyroid conditions and breast cancer prognosis in women undergoing endocrine therapy. The review will cover observational studies, cohort analyses, mechanistic insights, and experimental data that explore how hypothyroidism influences treatment outcomes such as recurrence rates, disease-free survival, and overall survival. Emphasis will be placed on both treated and untreated hypothyroid states, interaction with hormonal therapies, and receptor-mediated mechanisms.

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This review includes studies published within the last five years to ensure contemporary relevance and will prioritize findings from large cohort studies, population-based databases, and mechanistic research. Papers included must address either the incidence, prognosis, or therapy outcomes of breast cancer in the presence of hypothyroidism, focusing particularly on those patients undergoing endocrine therapy.

The significance of this review lies in its potential to clarify an understudied but clinically important intersection between thyroid dysfunction and breast cancer management. By elucidating this relationship, the review aims to inform clinical guidelines, optimize endocrine therapy regimens, and suggest areas for future investigation, including the necessity for personalized thyroid monitoring and management in breast cancer patients. Ultimately, this review seeks to provide oncologists and endocrinologists with an integrated understanding of how thyroid status may influence breast cancer prognosis and guide safer, more effective treatment strategies.

THEMATIC DISCUSSION:

Radiation-Induced Hypothyroidism in Breast Cancer Patients

One of the most consistent findings across studies is the increased risk of hypothyroidism in breast cancer patients receiving regional radiotherapy, particularly supraclavicular nodal irradiation. Research shows that radiation doses to the thyroid gland correlate with a higher incidence of clinical and subclinical hypothyroidism. Park et al. observed that the incidence of hypothyroidism was significantly higher in radiated patients compared to those not receiving radiation (9). Similarly, Digkas et al. identified nodal irradiation as a major risk factor, increasing the long-term risk of thyroid dysfunction post-treatment (10). Meta-analyses confirm this trend, reinforcing the importance of thyroid gland contouring and dose limitation in radiation planning (11).

Biological Influence of Hypothyroidism on Tumor Microenvironment

Emerging preclinical data suggest that thyroid hormones modulate the tumor microenvironment, influencing tumor progression and metastasis. Sterle et al. reported that hypothyroidism in murine models delayed primary tumor growth but paradoxically promoted lung metastases due to altered immune regulation, including increased regulatory T cells and pro-metastatic cytokines (12). This dualistic role highlights the complexity of systemic hypothyroidism, which may simultaneously suppress tumor proliferation while enhancing metastatic potential.

Thyroid Hormone Replacement Therapy (THRT) and Prognostic Implications

Thyroid hormone replacement, particularly levothyroxine (T4), may influence breast cancer outcomes through its interaction with estrogen receptor pathways. Some evidence suggests that T4 can enhance mitogenic signaling in ER-positive tumors, possibly reducing the efficacy of endocrine therapies like aromatase inhibitors. A phase II pilot study by Trehan et al. introduced the concept of euthyroid hypothyroxinemia using T3 as an alternative, showing promising progression-free survival with minimal adverse effects (13). However, larger studies are required to validate these preliminary findings and assess long-term safety and efficacy.

Inconsistencies in Prognostic Impact of Hypothyroidism

Despite biological plausibility, population-based data yield inconsistent conclusions regarding the impact of hypothyroidism on breast cancer-specific survival. McVicker et al. found no significant difference in overall or cancer-specific mortality between hypothyroid and euthyroid patients (14). In contrast, Elgebaly et al. reported that hypothyroid individuals had more aggressive disease features and poorer outcomes (15). These discrepancies may be attributed to variations in study populations, thyroid status definitions, and cancer subtypes.

Predictive Modeling of Radiation-Induced Thyroid Dysfunction

Radiobiological models are being developed to predict the risk of hypothyroidism based on radiation dosimetry. Huang et al. proposed a Normal Tissue Complication Probability (NTCP) model, suggesting that maintaining >8.5 cc of thyroid volume under 20 Gy keeps hypothyroidism risk below 15% (16). These tools can inform personalized radiation plans, balancing oncologic control with endocrine preservation.

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Oxidative Stress and Genomic Instability in Hypothyroid States

Experimental studies suggest that hypothyroidism may increase oxidative stress and DNA damage in mammary cells. Peixoto et al. demonstrated that hypothyroid rats exhibited elevated reactive oxygen species and genomic instability in breast tissue, which could predispose to malignancy or worsen prognosis in existing cancers (17). While not yet confirmed in clinical populations, these mechanistic insights highlight the broader systemic effects of thyroid dysfunction.

Table 1. Summary of Key Studies on the Impact of Hypothyroidism on Breast Cancer Prognosis During Endocrine Therapy

Study	Study Design	Sample Size	Key Findings
Park et al. (2022)	Population-based cohort	24567	Increased risk of hypothyroidism with radiation
Digkas et al. (2023)	Population-based cohort	18753	Nodal radiation associated with 68% higher hypothyroidism risk
Trehan et al. (2023)	Phase II pilot trial	7	T3 therapy showed 71% PFS at 9 months
McVicker et al. (2022)	UK population-based study	33418	No significant link between hypothyroidism and mortality
Elgebaly et al. (2021)	Observational cohort	128	Hypothyroidism linked with worse tumor grade and outcomes

Table 2. Incidence and Clinical Risk of Hypothyroidism Based on Radiation Dose to the Thyroid Gland

Radiation Dose Group (Gy)	Incidence of Hypothyroidism (%)	Recommended Clinical Action
<10 Gy	5	Low risk, standard monitoring
10-20 Gy	12	Moderate risk, consider thyroid-sparing
20-30 Gy	20	High risk, monitor TSH every 6 months
>30 Gy	26	Very high risk, thyroid contouring essential

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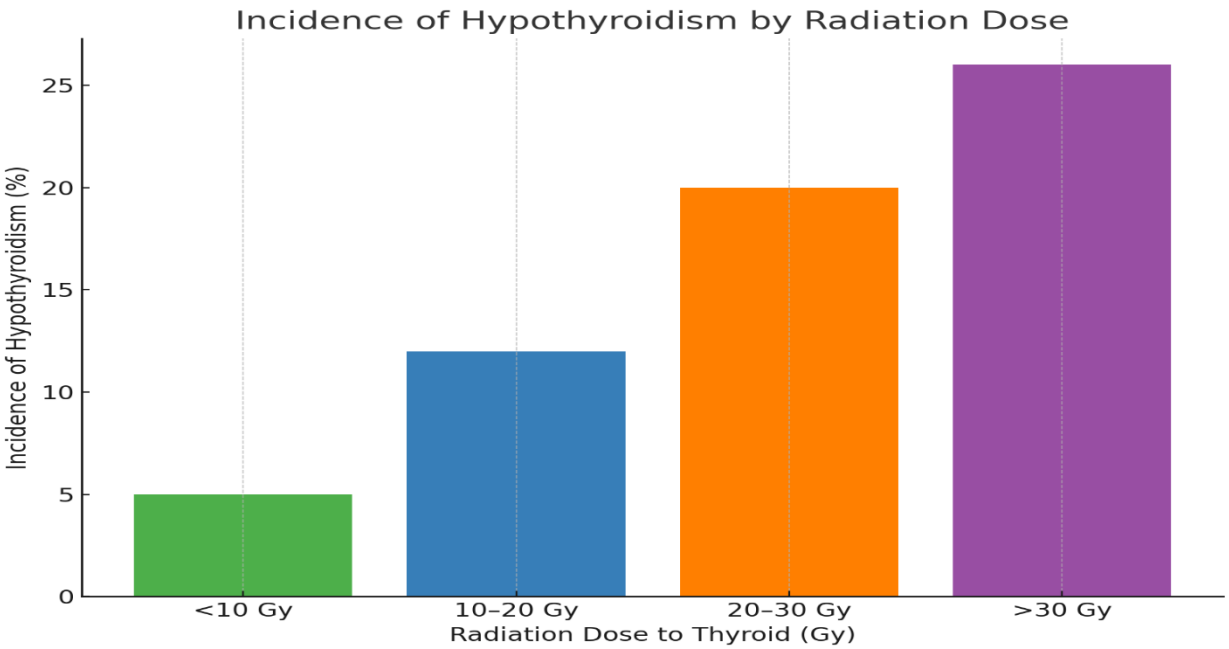


Figure 1Incidence of Hypothyroidism by Radiation Dose

CRITICAL ANALYSIS AND LIMITATIONS:

The current literature investigating the association between hypothyroidism and breast cancer prognosis during endocrine therapy reflects a diverse and growing body of research, yet it is not without substantial limitations. One of the most notable issues is the dominance of observational study designs, with a distinct scarcity of randomized controlled trials (RCTs). Many studies are either retrospective cohort analyses or case-control designs, which, while valuable for hypothesis generation, limit the strength of causal inferences. For instance, the B-TREUH pilot study, while novel in its approach of transitioning patients from levothyroxine (T4) to triiodothyronine (T3), enrolled only seven participants and lacked a control group, limiting both statistical power and the ability to generalize findings beyond the study population (18).

Small sample sizes further undermine the robustness of many findings. This is particularly problematic in subgroup analyses where the number of patients with both breast cancer and hypothyroidism becomes too limited to detect meaningful differences. For example, a population-based analysis examining radiation-induced hypothyroidism in breast cancer patients showed increased risk but lacked adjustment for critical variables such as baseline thyroid function and precise radiation dosimetry in all cases, which limits interpretability (19). Similarly, several radiobiological modeling studies evaluating thyroid dose-volume effects on hypothyroidism development have included fewer than 100 participants, raising concerns regarding the external validity of the generated thresholds and parameters (20).

Bias and confounding are also prevalent. Selection bias is introduced when studies include only survivors or those receiving specific therapies, thus omitting patients with more aggressive disease or differing comorbidity profiles. Additionally, confounding by indication is a major concern in studies evaluating thyroid hormone replacement therapy (THRT), as patients who receive THRT may differ systematically in health status, cancer stage, or healthcare access from those who do not. Performance bias is evident in some prospective studies that did not implement blinding or standardized outcome assessments, potentially influencing reported endpoints.

Another methodological concern is the variability in outcome definitions and measurement tools across studies. The definition of hypothyroidism varies—ranging from clinical diagnosis, biochemical thresholds (TSH elevation alone or in combination with T4 suppression), to prescription of THRT. Likewise, breast cancer prognosis has been evaluated using disparate endpoints including

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recurrence, progression-free survival, overall survival, and surrogate markers, making direct comparisons across studies challenging. This inconsistency affects not only the pooling of data for meta-analyses but also the translational applicability of findings to clinical practice (21).

Publication bias likely further distorts the body of evidence. Negative or null results are underreported, particularly in smaller or single-institution studies. For instance, while some large datasets report no significant relationship between hypothyroidism and breast cancer-specific mortality, these findings are less commonly emphasized in literature compared to studies reporting associations—suggesting a potential for skewed representation of outcomes in published research (22).

The generalizability of findings is another limitation. Many studies originate from specific geographic regions, such as European or East Asian cohorts, and findings often reflect region-specific treatment patterns, genetic backgrounds, and healthcare systems. A meta-analysis highlighted that hypothyroidism appeared to confer a reduced risk of breast cancer only in European populations, with no such association found in non-European groups—highlighting the importance of context in interpreting results (23). Additionally, few studies include racially or ethnically diverse populations, limiting the applicability of conclusions to global breast cancer populations.

Moreover, the heterogeneity in endocrine therapy regimens (e.g., tamoxifen versus aromatase inhibitors) is often not accounted for when assessing interactions with thyroid dysfunction. This variability in treatment exposure can significantly influence outcomes and may confound any observed associations with thyroid status. Studies that fail to stratify by endocrine therapy type or treatment adherence risk conflating the effect of thyroid dysfunction with the effect of breast cancer therapy itself (24).

Lastly, there is insufficient integration of mechanistic data into clinical research. While animal models and molecular studies suggest thyroid hormones modulate tumor microenvironment and metastatic behavior, these insights are rarely incorporated into prospective clinical trial designs. This disconnection between bench and bedside hinders a comprehensive understanding of how thyroid dysfunction mechanistically affects breast cancer progression, limiting opportunities to translate findings into therapeutic strategies (25).

In summary, while existing literature provides valuable insights into the potential influence of hypothyroidism on breast cancer prognosis during endocrine therapy, it is constrained by methodological weaknesses, inconsistent outcome measures, and limited generalizability. Addressing these limitations through well-powered, longitudinal studies with standardized definitions and diverse cohorts will be essential for drawing clinically actionable conclusions.

IMPLICATIONS AND FUTURE DIRECTIONS:

The implications of the association between hypothyroidism and breast cancer prognosis in patients receiving endocrine therapy are increasingly relevant to clinical practice, particularly as survival rates improve and treatment plans grow more complex. For clinicians, one of the most immediate takeaways is the need for proactive thyroid function monitoring in breast cancer patients, especially those receiving radiation to the supraclavicular region. Several recent studies have demonstrated a clear relationship between cumulative radiation dose and the risk of both subclinical and overt hypothyroidism, with incidence rates reaching as high as 26% within two years of therapy, particularly when thyroid mean dose exceeds 21 Gy (26,27). This suggests that integrating routine thyroid function testing—beginning six months post-treatment—could help mitigate endocrine complications and preserve long-term quality of life.

In terms of treatment planning, radiation oncologists may need to consider the thyroid gland as an organ at risk (OAR) during contouring and dosimetry, particularly in patients undergoing supraclavicular nodal irradiation. The implementation of dosimetric thresholds such as maintaining mean thyroid dose below 21 Gy or preserving a minimum volume of the thyroid from high-dose exposure may help minimize late thyroid toxicity (28). Policy-level changes, such as guideline updates from radiation oncology societies or endocrine panels, should encourage standardized screening protocols for thyroid dysfunction in breast cancer survivors—an aspect currently underemphasized in most follow-up care models.

Another clinical implication lies in the consideration of thyroid hormone replacement therapy (THRT) itself. Although levothyroxine (T4) is the standard for managing hypothyroidism, emerging evidence from early-phase studies suggests that T4 may have mitogenic and pro-oncogenic effects in estrogen receptor-positive (ER+) breast cancer patients, potentially antagonizing endocrine therapies like aromatase inhibitors. This has led to interest in the selective use of triiodothyronine (T3), which appears to have a less aggressive profile, though data remain preliminary (29). The safety and efficacy of switching from T4 to T3 in cancer patients with hypothyroidism require further evaluation but could potentially lead to a paradigm shift in endocrine management for this subpopulation.

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Despite accumulating evidence, key research gaps remain. The lack of large-scale randomized controlled trials examining the direct impact of thyroid dysfunction and THRT on breast cancer prognosis is a major limitation. While some observational studies report no significant association between hypothyroidism and cancer-specific mortality, others suggest adverse outcomes with T4 use, especially in hormone-sensitive tumors (30). These inconsistencies underscore the need for prospective, multicenter studies with stratification by hormone receptor status, thyroid function state, and type of endocrine therapy used.

Additionally, mechanistic insights into the interaction between thyroid hormones and estrogen pathways at the molecular level are still emerging. Preclinical models suggest a cross-talk between thyroid hormone receptors and estrogen receptors that may drive oncogenic signaling and alter treatment response (31). However, translating these findings into clinical biomarkers or therapeutic targets requires further translational research. Integrating thyroid receptor expression profiles into tumor phenotyping may eventually help personalize treatment for breast cancer patients with concurrent thyroid dysfunction.

Future research should prioritize longitudinal cohort studies with extended follow-up, standardized definitions for thyroid dysfunction, and comprehensive hormone receptor profiling. Randomized trials comparing T3 versus T4 in breast cancer patients with hypothyroidism could offer definitive evidence on the safest and most effective hormone replacement strategy. Furthermore, incorporating thyroid-related endpoints into breast cancer trials may uncover previously overlooked toxicities or prognostic modifiers. The development of integrated clinical pathways that include endocrinologists in oncology care teams will also be essential to ensure a multidisciplinary approach to survivorship.

Overall, this narrative review highlights the clinical importance of thyroid health in the management of breast cancer and underscores a pressing need for interdisciplinary guidelines and focused research efforts to optimize outcomes in this patient population.

CONCLUSION:

This narrative review highlights the nuanced and multifaceted relationship between hypothyroidism and breast cancer prognosis in patients undergoing endocrine therapy. The current evidence suggests that radiation therapy, particularly involving the supraclavicular field, significantly increases the risk of hypothyroidism, which in turn may subtly influence treatment outcomes. While some data suggest a potential interplay between thyroid hormone replacement—particularly levothyroxine—and estrogen receptor signaling, the clinical implications remain inconclusive due to variability in study designs, endpoints, and populations. Overall, the strength of evidence is moderate, with most findings derived from observational cohorts and limited prospective data. Clinicians should consider routine thyroid function monitoring as part of survivorship care, and radiation planning should aim to spare thyroid tissue when feasible. Future research should focus on high-quality, prospective trials that explore the biological mechanisms, treatment interactions, and long-term outcomes associated with thyroid dysfunction in this population. Such studies are crucial for developing evidence-based guidelines and ensuring holistic, endocrine-informed cancer care.

AUTHOR CONTRIBUTION

Author	Contribution
Irfan Ishaque*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zainab Zikria	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Maida Zafar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published

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Ramaz Rashid	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Eman Aslam	Contributed to study concept and Data collection Has given Final Approval of the version to be published
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